



STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 103835

TO: Sabiha Qazi
Location: CM-1/2D19
Art Unit: 1616
Friday, September 26, 2003
Case Serial Number: 09/899702

From: Paul Schulwitz
Location: Biotech-Chem Library
CM1-6B06
Phone: 305-1954

paul.schulwitz@uspto.gov

Search Notes

Examiner Qazi,

See attached results.

If you have any questions about this search feel free to contact me at any time.

Thank you for using STIC search services!

Paul Schulwitz
Technical Information Specialist
STIC Biotech/Chem Library
(703)305-1954

Paul Schultzy please

Access DB# 103835

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: SABITA GAZ Examiner #: 74141 Date: 9/12/03
Art Unit: 1616 Phone Number 305-390 Serial Number: 91899,702
Mail Box and Bldg/Room Location: 2 D19 Results Format Preferred (circle) PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Estrogenic Compds as antiangiogenic agents
Inventors (please provide full names): ROBERT DAMATO

Earliest Priority Filing Date: 7/5/2001

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search for the compds of

cl 1, 2, 7, 8, 9, 10,

29

+

30

Please note Rg is always 014.
+ R0+Rb are always H.

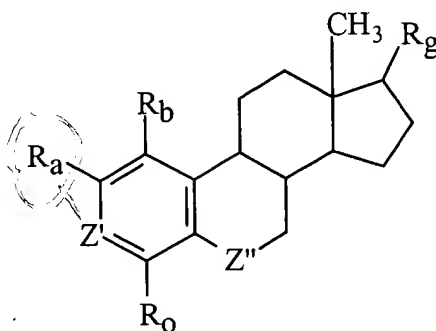
STAFF USE ONLY

	Type of Search	Vendors and cost where applicable.
Searcher: _____	NA Sequence (#) _____	STN <u>988.94</u>
Searcher Phone #: _____	AA Sequence (#) _____	Dialog _____
Searcher Location: _____	Structure (#) <u>7</u>	Questel/Orbit _____
Date Searcher Picked Up: <u>9/17</u>	Bibliographic _____	Dr.Link _____
Date Completed: <u>9/26</u>	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: <u>60</u>	Fulltext _____	Sequence Systems _____
Clerical Prep Time: _____	Patent Family _____	WWW/Internet _____
Online Time: <u>105</u>	Other _____	Other (specify) _____

Amendments to the Claims

Please amend the claims as indicated below.

1. (Presently Amended) A compound of the general formula:



wherein:

a) R_b and R_o are independently ~~both, -H, -Cl, -Br, -I, -F, -CN, lower alkyl, -OH, -CH₂-OH, -NH₂, or -N(R₆)(R₇), wherein R₆ and R₇ are independently hydrogen or an alkyl or branched alkyl with up to 6 carbons;~~

b) R_a is -N₃, -C≡N, -C≡C-R, -CH=CH-R, -R-CH=CH₂, -C≡CH, -O-R, -R-R₁, or -O-R-R₁ where R is a straight or branched alkyl with up to 10 carbons or aralkyl, and R_1 is -OH, -NH₂, -Cl, -Br, -I, -F or CF₃;

c) Z' is >CH, ~~>C(OH),~~ or >C-R₂-OH, where R₂ is an alkyl or branched alkyl with up to 10 carbons or aralkyl;

d) >C-R_g is ~~>C(H)-OH,~~ and

e) Z'' is ~~>CH₂,~~ >C=O, >C(H)-OH, >C=N-OR₅, >C(H)-C≡N, or >C(H)-NR₅R₅, wherein each R₅ is independently hydrogen, an alkyl or branched alkyl with up to 10 carbons or aralkyl;

with the proviso that if R_b is H, R_e is H, Z' is $>C(OH)$, $>C-R_g$ is $>C(H)OH$, do

Z'' is $>CH_2$, then R_a is neither OCH_3 nor OCH_2CH_3 , not $=OR$ and R_1 is not CF_3 . ?

2. (Presently amended) The compound of Claim 1, wherein:

R_b and R_e are H,

R_a is $-C \equiv C-CH_3$; and

Z' is $>C(OH)$,

Z'' is $>CH_2$.

- 3-4. (Withdrawn).

- 5-6. (Canceled).

7. (Presently amended) The compound of Claim 1, wherein:

R_b and R_e are H,

R_a is $CH=CH_2$

Z' is $>C(OH)$, and

Z'' is $>CH_2$.

8. (Presently amended) The compound of Claim 1, wherein:

R_b and R_e are H,

R_a is $E-CH=CH(CH_3)$

Z' is $>C(OH)$, and

Z'' is $>CH_2$.

9. (Presently amended) The compound of Claim 1, wherein:

R_b and R_e are H,

R_a is NHC_2H_5

Z' is >C-OH , and

Z'' is >CH_2 .

10. (Presently amended) The compound of Claim 1, wherein:

R_b and R_e are H;

R_d is NHCOCH_3

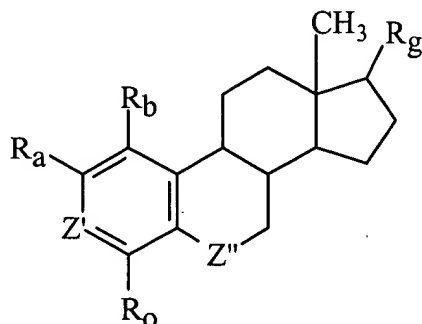
Z' is >C-OH , and

Z'' is >CH_2 .

11-14. (Canceled).

15-28. (Withdrawn).

29. (Presently amended) A compound of the general formula:



wherein:

a) ~~R_b and R_o are independently both -H, -Cl, -Br, -I, -F, -CN, lower alkyl, -OH, -CH₂-OH, -NH₂, or N(R₆)(R₇), wherein R₆ and R₇ are independently hydrogen or an alkyl or branched alkyl with up to 6 carbons;~~

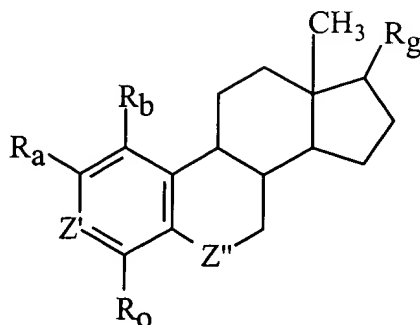
~~b) R_a is NHCOCH₃;~~

~~c) Z' is >CH-, >COH-, or >C-R₂-OH, where R₂ is an alkyl or branched alkyl with up to 10 carbons or aralkyl;~~

~~d) >C-R_g is >C(H)-OH;~~ and

~~e) Z'' is >CH₂-, >C=O-, >C(H)-OH-, >C=N-OH-, >C=N-OR₅-, >C(H)-C≡N-, or >C(H)-NR₅R₅-, wherein each R₅ is independently hydrogen, an alkyl or branched alkyl with up to 10 carbons or aralkyl.~~

30. (Presently amended) A compound of the general formula:



wherein:

a) R_b and R_o are independently both ~~H, Cl, Br, I, F, CN, lower alkyl, OH, CH₂OH, NH₂, or N(R₆)(R₇), wherein R₆ and R₇ are independently hydrogen or an alkyl or branched alkyl with up to 6 carbons;~~

b) R_a is ~~O-R-R₁~~ where R is a straight or branched alkyl with up to 10 carbons or aralkyl, and R_1 is -OH, -NH₂, -Cl, -Br, -I, -F or CF₃;

c) Z' is ~~CH₂~~COH, or $>C-R_2-OH$, where R_2 is an alkyl or branched alkyl with up to 10 carbons or aralkyl;

d) $>C-R_g$ is ~~>C(H)-OH~~; and

e) Z'' is ~~>CH₂~~, $>C=O$, $>C(H)-OH$, $>C-N-OH$, $>C-N-OR_5$, $>C(H)-C\equiv N$, or $>C(H)-NR_5R_5$, wherein each R_5 is independently hydrogen, an alkyl or branched alkyl with up to 10 carbons or aralkyl;

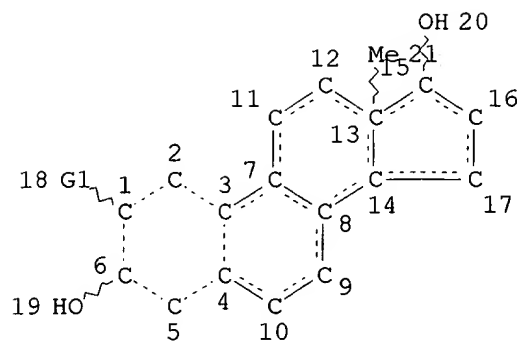
with the proviso that if R_b is H, R_o is H, Z' is $>COH$, and Z'' is $>CH_2$, then

R_a ~~is not~~ $-OCH_2CF_3$, CF_3 .

=> d que 111

L1

STR



$$\begin{array}{c} \text{N} \sim \text{N} \sim \text{N} \\ @22 \ 23 \ 24 \end{array}$$

$$\begin{array}{c} \text{C} \equiv \text{C} \sim \text{G2} \\ @25 \ 26 \ 27 \end{array}$$

Ak @

$$\begin{array}{c} \text{CH} \equiv \text{CH} \sim \text{G2} \\ @28 \ 29 \ 30 \end{array}$$

$$\begin{array}{c} \text{Ak} \sim \text{CH} \equiv \text{CH2} \\ @31 \ 32 \ 33 \end{array}$$

$$\begin{array}{c} \text{Ak} \sim \text{Cb} \sim \text{CH} \equiv \text{CH2} \\ @34 \ 35 \ 36 \ 37 \end{array}$$

$$\begin{array}{c} \text{C} \equiv \text{CH} \\ @38 \ 39 \end{array}$$

$$\begin{array}{c} \text{O} \sim \text{G2} \\ @40 \ 41 \end{array}$$

$$\begin{array}{c} \text{Ak} \sim \text{G3} \\ @42 \ 43 \end{array}$$

$$\begin{array}{c} \text{Ak} \sim \text{Cb} \sim \text{G3} \\ @44 \ 45 \ 46 \end{array}$$

$$\begin{array}{c} \text{O} \sim \text{Ak} \sim \text{G3} \\ @47 \ 48 \ 49 \end{array}$$

$$\begin{array}{c} \text{O} \sim \text{Ak} \sim \text{Cb} \sim \text{G3} \\ @50 \ 51 \ 52 \ 53 \end{array}$$

$$\begin{array}{c} \text{N} \sim \text{Et} \\ @54 \ 55 \end{array}$$

$$\begin{array}{c} \text{Ak} \sim \text{Cb} \\ @61 \ 62 \\ \text{O} \\ \text{||} \end{array}$$

Page 1-A

60

Page 1-B

$$\begin{array}{c} \text{N} \sim \text{C} \sim \text{Me} \\ @56 \ 57 \ 58 \end{array}$$

Page 2-A

VAR G1=22/CN/25/28/31/34/38/40/42/44/47/50/54/56

VAR G2=60/61

VAR G3=OH/NH2/X/CF3

NODE ATTRIBUTES:

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CONNECT IS E2 RC AT 5
CONNECT IS E2 RC AT 10
CONNECT IS E2 RC AT 31
CONNECT IS E2 RC AT 34
CONNECT IS E2 RC AT 35
CONNECT IS E2 RC AT 42
CONNECT IS E2 RC AT 44
CONNECT IS E2 RC AT 45
CONNECT IS E2 RC AT 48

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CONNECT IS E2 RC AT 51
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 CONNECT IS E2 RC AT 54
 CONNECT IS E2 RC AT 56
 CONNECT IS E1 RC AT 60
 CONNECT IS E2 RC AT 61
 CONNECT IS E1 RC AT 62
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 GGCAT IS UNS AT 35
 GGCAT IS UNS AT 45
 GGCAT IS UNS AT 52
 GGCAT IS UNS AT 62
 DEFAULT ECLEVEL IS LIMITED
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 ECOUNT IS M6 C AT 45
 ECOUNT IS M6 C AT 52
 ECOUNT IS M6 C AT 62

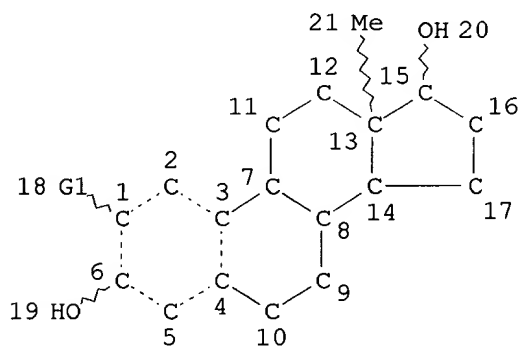
GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

L3 99 SEA FILE=REGISTRY SSS FUL L1

L9 STR



N~N~N
 @22 23 24

C≡C~G2
 @25 26 27

Ak @

CH≡CH~G2
 @28 29 30

Ak~CH≡CH2
 @31 32 33

Ak~Cb~CH≡CH2
 @34 35 36 37

C≡CH
 @38 39

O~G2
 @40 41

Ak~G3
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Ak~Cb~G3
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O~Ak~G3
 @47 48 49

O~Ak~Cb~G3
 @50 51 52 53

N~Et
 @54 55

Ak~Cb
 @61 62
 O
 ||

Page 1-B

|||
N~C~Me
@56 57 58

Page 2-A

VAR G1=22/CN/25/28/31/34/38/40/42/44/47/50/54/56

VAR G2=60/61

VAR G3=OH/NH2/X/CF3

NODE ATTRIBUTES:

CONNECT IS E2 RC AT 2
CONNECT IS E2 RC AT 5
CONNECT IS E2 RC AT 9
CONNECT IS E2 RC AT 10
CONNECT IS E2 RC AT 11
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DEFAULT MLEVEL IS ATOM
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GGCAT IS UNS AT 45
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DEFAULT ECLEVEL IS LIMITED
ECOUNT IS M6 C AT 35
ECOUNT IS M6 C AT 45
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GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

L10 40 SEA FILE=REGISTRY SUB=L3 SSS FUL L9

L11 448 SEA FILE=HCAPLUS ABB=ON PLU=ON L10

=> d:ibib ab hitstr.l11-1-10 200-210 435-448

L11 ANSWER 1 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:648310 HCAPLUS
DOCUMENT NUMBER: 139:180232
TITLE: Preparation of 2-methoxyestradiol and its anticancer activity
INVENTOR(S): Wang, Jie; Li, Zhongyi; Chen, Linsheng
PATENT ASSIGNEE(S): Weixing Inst. of Biological Products, Liaoning, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 7 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1354184	A	20020619	CN 2000-123346	20001130

PRIORITY APPLN. INFO.: CN 2000-123346 20001130

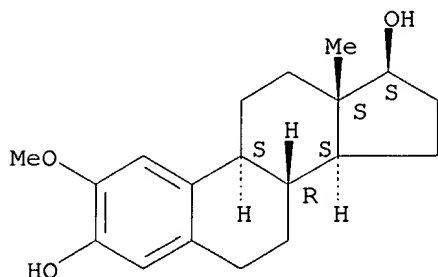
AB Title compd. was prepd. from estradiol via protection of hydroxy group (such as alkyl, aryl, acyl, or substituted silyl), then halogenated to obtained 2-haloestradiol diether; further treated with Bu lithium, reacted with dimethy formamide and hydrolyzation with acid, gave 2-formylestradiol diether; after redn. and deprodn, got the title product. Title compd. can be prepd. as injection, capsule, or tablet for treating neoplasm (such as lung neoplasm, breast neoplasm, melanoma, prostate neoplasm, pancreatic neoplasm, brain neoplasm, etc).

IT **362-07-2P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(of 2-methoxyestradiol and its anticancer activity)

RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 2 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:570754 HCAPLUS
DOCUMENT NUMBER: 139:111707
TITLE: Methods and compositions for stimulating bone growth using inhibitors of microtubule assembly
INVENTOR(S): Chen, Di; Rossini, Jorge Gianni; Zhao, Ming; Qiao, Mei; Mundy, Gregory R.

PATENT ASSIGNEE(S): Osteoscreen, Inc., USA
 SOURCE: PCT Int. Appl., 30 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003059277	A2	20030724	WO 2003-US1264	20030114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

US 2003181374 A1 20030925 US 2003-345112 20030114

PRIORITY APPLN. INFO.: US 2002-348762P P 20020114

AB The invention discloses compns. and methods for use in treating skeletal system disorders in a vertebrate at risk for bone loss, and for treating conditions that are characterized by the need for bone growth, in treating fractures, and in treating cartilage disorders. More specifically, the invention discloses the use of inhibitors of microtubule assembly for enhancing bone growth. The microtubule inhibitors include e.g. TN16 [3-(1-anilinoethylidene)-5-benzylpyrrolidine-2,4-dione].

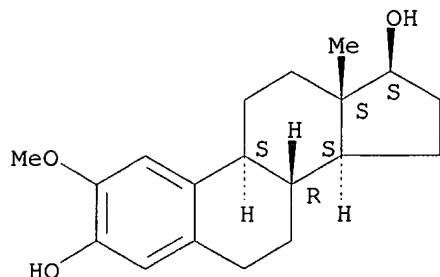
IT **362-07-2**, 2-Methoxyestradiol **362-07-2D**,
 2-Methoxyestradiol, analogs

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (microtubule inhibitors for stimulating bone growth)

RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

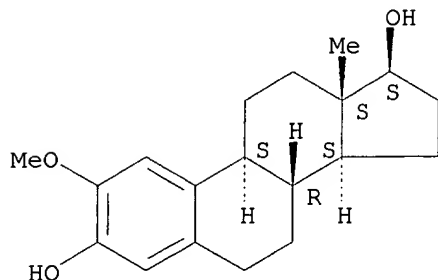
Absolute stereochemistry.



RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 3 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:532550 HCAPLUS

DOCUMENT NUMBER: 139:95434

TITLE: Chorioallantoic membrane (CAM) assay for identifying agents with biological effects

INVENTOR(S): Hazel, Susan Jane

PATENT ASSIGNEE(S): Medvet Science Pty. Ltd., Australia

SOURCE: PCT Int. Appl., 48 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055530	A1	20030710	WO 2002-AU1759	20021220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:

US 2001-343345P P 20011221

AU 2002-2002950565A 20020802

AU 2002-2002952008A 20021011

AB The invention discloses assays and, particularly, chorioallantoic membrane (CAM) assays for identifying and/or assessing agents with biol. effects (e.g. agents which effect angiogenesis, or promote neurogenesis, or which are capable of silencing particular gene(s)), and for assessing toxicity of various agents (e.g. for toxicity testing of candidate agents with desirable biol. effects). The CAM assay comprises (i) sep. placing 2-4 day old embryos from chicken or the like, which have been removed from their shells, into sep. cup means to support the embryos through steps (ii)-(vii), wherein each cup means also contains a suitable amt. of a growth medium; (ii) incubating the embryos for about 24 h; (iii) measuring

the size of the CAM developed from each embryo, and grouping the embryos having CAMs of substantially similar size; (iv) applying to one or more embryo(s) within a selected group, a candidate agent, wherein the candidate agent is applied to the/each embryo by absorbing the candidate agent onto a porous or otherwise sorbent support and placing the support into contact with the CAM such that at least a portion of the candidate agent thereafter diffuses from the support to the CAM; (v) incubating the embryo(s) of step (iv) and a control embryo(s) from the same selected group for about 18-24 h; (vi) administering to the CAM of each embryo of step (v) a contrasting compn. comprising skim milk or the like and a suitably colored dyestuff; and (vii) detg. whether the candidate agent affects the CAM and/or embryo by observing differences between the CAM(s) and/or embryo(s) to which the candidate agent was applied and the CAM(s) and/or embryo(s) of the control embryo(s) of the same selected group.

IT 362-07-2, 2-Methoxyestradiol

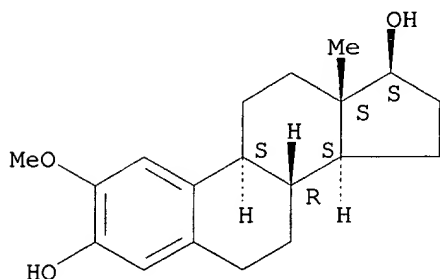
RL: PAC (Pharmacological activity); BIOL (Biological study)

(chorioallantoic membrane assay for identifying agents with biol. effects)

RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:532528 HCAPLUS

DOCUMENT NUMBER: 139:79109

TITLE: Use of UGT inhibitors to increase bioavailability

INVENTOR(S): Wachter, Vincent J.; Benet, Leslie Z.

PATENT ASSIGNEE(S): Avmax, Inc., USA

SOURCE: PCT Int. Appl., 92 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055494	A1	20030710	WO 2002-US41301	20021220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,				

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-342656P P 20011221

AB Methods for increasing the bioavailability of certain orally administered pharmaceutical compds. by the coadministration of inhibitors of UDP-glucuronosyltransferase (UGT) are disclosed. Particular combinations of UGT inhibitors and pharmaceutical compd. are described.

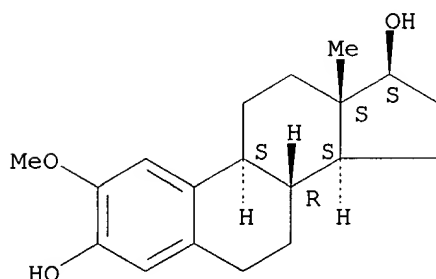
IT **362-07-2**, 2-Methoxyestradiol

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of UDP glucuronosyltransferase inhibitors to increase bioavailability of orally administered drugs)

RN 362-07-2 HCAPLUS

CN Estr-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:480509 HCAPLUS

DOCUMENT NUMBER: 139:211848

TITLE: Roles of p38- and c-jun NH2-terminal kinase-mediated pathways in 2-methoxyestradiol-induced p53 induction and apoptosis

AUTHOR(S): Shimada, Keiji; Nakamura, Mitsutoshi; Ishida, Eiwa; Kishi, Munehiro; Konishi, Noboru

CORPORATE SOURCE: Department of Pathology, Nara Medical University, Kashihara, Nara, 634-8521, Japan

SOURCE: Carcinogenesis (2003), 24(6), 1067-1075
CODEN: CRNGDP; ISSN: 0143-3334

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB As 2-methoxyestradiol (2-ME), an endogenous estrogen metabolite, has been established to cause apoptosis of prostate cancer cells, the downstream

effectors of the signaling remain unclear. In the current study, we investigated mol. mechanisms by which 2-ME induces apoptosis in human prostate cancer cell line, LNCaP. It was found that 2-ME mediates apoptosis through p53 induction. Nuclear factor kappaB (NF.kappa.B) was activated by 2-ME and closely regulated by the mitogen-activated protein kinase, p38. Inhibition of p38 or NF.kappa.B resulted in suppression of p53 induction and apoptosis. Moreover, we demonstrated that 2-ME activates the c-jun NH2-terminal kinase (JNK)/activation protein (AP)-1 pathway. Interestingly, inhibition of JNK strongly reduced Bcl-2 phosphorylation by 2-ME as well as p53 induction, and almost completely suppressed 2-ME-induced apoptosis. Androgen stimulation with dihydrotestosterone, a major endogenous metabolite of testosterone, also significantly inhibited p38/NF.kappa.B and JNK/AP-1 activation and apoptosis. The results suggest that not only p53 induction through p38/JNK-dependent NF.kappa.B/AP-1 activation but also JNK-dependent Bcl-2 phosphorylation are required for 2-ME-induced apoptosis; moreover, inhibition of these pathways may be involved in androgen-mediated resistance to apoptosis.

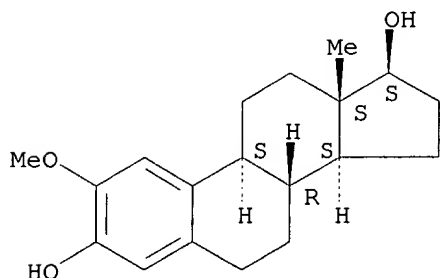
IT 362-07-2, 2-Methoxyestradiol

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(roles of p38- and c-jun NH2-terminal kinase-mediated pathways in
2-methoxyestradiol-induced p53 induction and apoptosis in human
prostate cancer LNCaP cells)

RN 362-07-2 HCAPLUS

CN Estr-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX
NAME)

Absolute stereochemistry.



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:442317 HCAPLUS

DOCUMENT NUMBER: 139:207954

TITLE: Endogenous estradiol metabolites stimulate the in
vitro proliferation of human osteoblastic cells

AUTHOR(S): Seeger, H.; Hadji, P.; Mueck, A. O.

CORPORATE SOURCE: Section of Endocrinology and Menopause, Women's
University Hospital, Tubingen, D-72076, Germany

SOURCE: International Journal of Clinical Pharmacology and
Therapeutics (2003), 41(4), 148-152

CODEN: ICTHEK; ISSN: 0946-1965

PUBLISHER: Dustri-Verlag Dr. Karl Feistle

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Evidence is accumulating that estradiol metabolites are not merely waste products but may play physiol. and pathophysiol. roles. In the present study, effect of estradiol metabolites on the proliferation of human female osteoblasts was investigated for the first time and compared to effect of their parent substance 17. β -estradiol. Osteoblasts from female hipbone were incubated with estradiol and estradiol metabolites at dosages of 10^{-9} , 10^{-7} and 10^{-5} M for 7 days. Cell proliferation was measured using a cell counter. Estradiol had no effect on cell proliferation at the tested concns. In contrast, the A-ring metabolites 2-hydroxyestrone, 2-hydroxyestradiol, 2-hydroxyestriol, 4-hydroxyestrone and 4-hydroxyestradiol displayed significant increases in cell proliferation, although only at high physiol. or pharmacol. dosages. Methylation of these metabolites completely abolished their proliferating property. For the D-ring metabolites estrone, estriol, estetrol and 16. α -hydroxyestrone, no significant changes in cell proliferation were obsd. The present results suggest that endogenous estradiol metabolites are capable of stimulating the proliferation of human female osteoblastic cells. None of the estradiol metabolites examd. inhibited cell proliferation. Thus, estradiol metab. may play a decisive role in development and maintenance of bone mass.

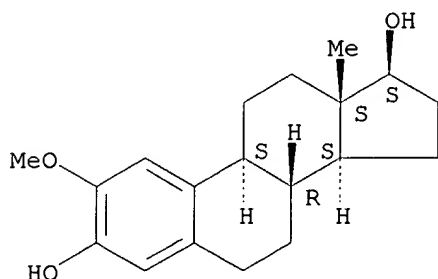
IT 362-07-2, 2-Methoxyestradiol

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(endogenous estradiol metabolites stimulate in vitro proliferation of human osteoblastic cells)

RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17. β .)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:405497 HCAPLUS

DOCUMENT NUMBER: 139:207264

TITLE: Free radical stress in chronic lymphocytic leukemia cells and its role in cellular sensitivity to ROS-generating anticancer agents

AUTHOR(S): Zhou, Yan; Hileman, Elizabeth O.; Plunkett, William; Keating, Michael J.; Huang, Peng

CORPORATE SOURCE: Departments of Molecular Pathology, Experimental Therapeutics, and Leukemia, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA

SOURCE: Blood (2003), 101(10), 4098-4104
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 2-Methoxyestradiol (2-ME), a new anticancer agent currently in clin. trials, has been demonstrated to inhibit superoxide dismutase (SOD) and to induce apoptosis in leukemia cells through a free radical-mediated mechanism. Because the accumulation of superoxide (O_2^-) by inhibition of SOD depends on the cellular generation of O_2^- , we hypothesized that the endogenous prodn. of superoxide may be a crit. factor that affects the antileukemia activity of 2-ME. In the present study, we investigated the relationship between cellular O_2^- contents and the cytotoxic activity of 2-ME in primary leukemia cells from 50 patients with chronic lymphocytic leukemia (CLL). Quantitation of O_2^- revealed that the basal cellular O_2^- contents are heterogeneous among patients with CLL. The O_2^- levels were significantly higher in CLL cells from patients with prior chemotherapy. CLL cells with higher basal O_2^- contents were more sensitive to 2-ME in vitro than those with lower O_2^- contents. There was a significant correlation between the 2-ME-induced O_2^- increase and the loss of cell viability. Importantly, addn. of arsenic trioxide, a compd. capable of causing reactive oxygen species (ROS) generation, significantly enhanced the activity of 2-ME, even in the CLL cells that were resistant to 2-ME alone. These results suggest that the cellular generation of O_2^- plays an important role in the cytotoxic action of 2-ME and that it is possible to use exogenous ROS-producing agents such as arsenic trioxide in combination with 2-ME to enhance the antileukemia activity and to overcome drug resistance. Such a combination strategy may have potential clin. applications.

IT 362-07-2, 2-Methoxyestradiol

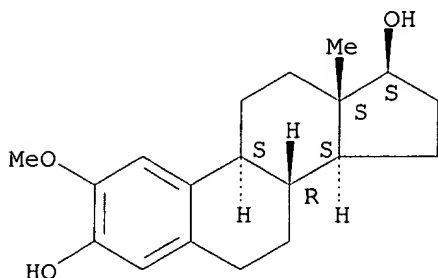
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(free radical stress in chronic lymphocytic leukemia cells and its role in cellular sensitivity to ROS-generating anticancer agents)

RN 362-07-2 HCAPLUS

CN Estr-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:374899 HCAPLUS

DOCUMENT NUMBER: 139:94639
TITLE: Novel therapies in multiple myeloma
AUTHOR(S): Singhal, Seema; Mehta, Jayesh
CORPORATE SOURCE: Multiple Myeloma Program, Division of
Hematology/Oncology, The Feinberg School of Medicine,
The Robert H. Lurie Comprehensive Cancer Center,
Northwestern University, Chicago, IL, 60611, USA
SOURCE: International Journal of Hematology (2003), 77(3),
226-231
CODEN: IJHEEY; ISSN: 0925-5710
PUBLISHER: Carden Jennings Publishing
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The discovery of the activity of thalidomide in myeloma in the late 1990s transformed the therapy of myeloma dramatically. Apart from providing a useful treatment option for patients with myeloma, it has spurred clin. investigation of several other nonchemotherapeutic agents for this disease. These active, promising agents include CC-5013 (a thalidomide analog) and bortezomib (a proteasome inhibitor), as well as other agents, such as arsenic trioxide, ENMD 0995 and 2-methoxyestradiol. Preliminary data show that a no. of these agents are active in treating disease that has relapsed after conventional chemotherapy as well as after high-dose therapy and transplantation, and some agents are active even after other novel agents have failed. The only novel drug that is com. available currently is thalidomide, which has a therapeutically relevant benefit at all stages of the disease. A therapeutic trial of thalidomide is essential for all patients with myeloma. There are in vitro and in vivo data showing synergy between some of the novel agents. Although these novel drugs are typically used for treating disease that is refractory to or has relapsed after cytotoxic therapy, it is likely that they will start being used as part of frontline therapy, either by themselves or in combination with chemotherapy.

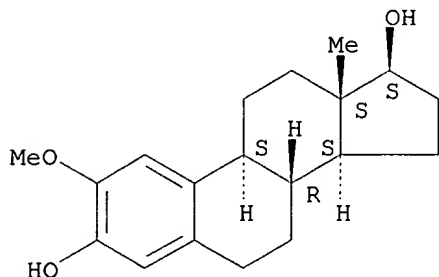
IT 362-07-2, 2-Methoxyestradiol

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(novel therapies in multiple myeloma)

RN 362-07-2 HCAPLUS

CN Estr-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX
NAME)

Absolute stereochemistry.



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:371246 HCAPLUS

DOCUMENT NUMBER: 139:211744

TITLE: Relative imbalances in estrogen metabolism and conjugation in breast tissue of women with carcinoma: potential biomarkers of susceptibility to cancer

AUTHOR(S): Rogan, Eleanor G.; Badawi, Alaa F.; Devanesan, Prabu D.; Meza, Jane L.; Edney, James A.; West, William W.; Higginbotham, Sheila M.; Cavalieri, Ercole L.

CORPORATE SOURCE: Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, 986805 Nebraska Medical Center, Omaha, NE, 68198-6805, USA

SOURCE: Carcinogenesis (2003), 24(4), 697-702

CODEN: CRNGDP; ISSN: 0143-3334

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Exposure to estrogens was assocd. with an increased risk of developing breast cancer. Breast biopsy tissues from 49 women without breast cancer (controls) and 28 with breast carcinoma (cases) were analyzed by HPLC with electrochem. detection for 31 estrogen metabolites and catechol estrogen quinone-glutathione conjugates. The levels of estrone and estradiol were higher in cases. More 2-catechol estrogen (CE) than 4-CE was obsd. in controls, but the 4-CE were three times higher than 2-CE in cases. In addn., the 4-CE were nearly four times higher in cases than in controls. Less O-methylation was obsd. for the CE in cases. The level of catechol estrogen quinone conjugates in cases was three times that in controls, suggesting in the cases a higher probability for the quinones to react with DNA and generate mutations that may initiate cancer. The levels of 4-CE and quinone conjugates were highly significant predictors of breast cancer. These results suggest that some catechol estrogen metabolites and conjugates could serve as biomarkers to predict risk of breast cancer.

IT 362-07-2

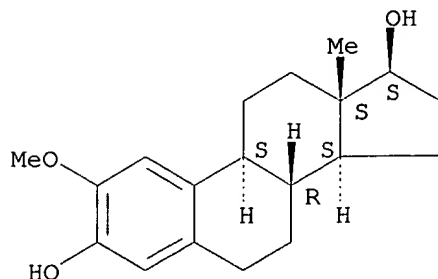
RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)

(estrogen metab. and conjugation imbalances in breast carcinoma potential biomarkers of susceptibility to cancer)

RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

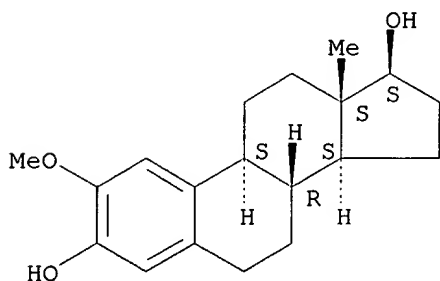


REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:366131 HCAPLUS
DOCUMENT NUMBER: 139:131348
TITLE: JNK-dependent Release of Mitochondrial Protein, Smac,
during Apoptosis in Multiple Myeloma (MM) Cells
AUTHOR(S): Chauhan, Dharminder; Li, Guilan; Hideshima, Teru;
Podar, Klaus; Mitsiades, Constantine; Mitsiades,
Nicholas; Munshi, Nikhil; Kharbanda, Surender;
Anderson, Kenneth C.
CORPORATE SOURCE: Dana Farber Cancer Institute, Department of Medical
Oncology, The Jerome Lipper Multiple Myeloma Center,
Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Journal of Biological Chemistry (2003), 278(20),
17593-17596
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular
Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Smac, second mitochondria-derived activator of caspases, promotes
apoptosis via activation of caspases. Previous studies have shown that
c-Jun NH2-terminal kinase (JNK) is involved in regulating another
mitochondrial protein, cytochrome c during apoptosis; however, the role of
JNK in the release of mitochondrial Smac is unknown. Here we show that
induction of apoptosis in multiple myeloma (MM) cells is assocd. with
activation of JNK, translocation of JNK from cytosol to mitochondria, and
release of Smac from mitochondria to cytosol. Blocking JNK either by
dominant-neg. mutant (DN-JNK) or cotreatment with a specific JNK
inhibitor, SP600125, abrogates both stress-induced release of Smac and
induction of apoptosis. These findings demonstrate that activation of JNK
is an obligatory event for the release of Smac during stress-induced
apoptosis in MM cells.
IT 362-07-2, 2-Methoxyestradiol
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological
activity); BIOL (Biological study)
(JNK-dependent release of mitochondrial protein, Smac, mitochondria to
cytosol during 2ME2- and PS-341-induced apoptosis in multiple myeloma
cells)
RN 362-07-2 HCAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX
NAME)

Absolute stereochemistry.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

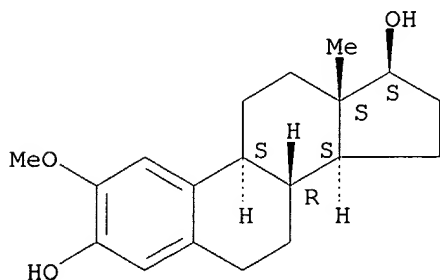
L11 ANSWER 200 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:220249 HCAPLUS
DOCUMENT NUMBER: 129:3702
TITLE: Structural analysis of an anti-estradiol antibody
AUTHOR(S): Lamminmaki, Urpo; Villoutreix, Bruno O.; Jauria, Piitu; Saviranta, Petri; Vihinen, Mauno; Nilsson, Lennart; Telemann, Olle; Lovgren, Timo
CORPORATE SOURCE: Dep. Biotechnol., Univ. Turku, Turku, FIN-20520, Finland
SOURCE: Molecular Immunology (1997), 34(16/17), 1215-1226
CODEN: MOIMD5; ISSN: 0161-5890
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An anti-estradiol antibody with improved specificity was searched for by combining steroid analog binding studies, mutant antibodies obtained from a phage-display library and structural modeling. Three-dimensional models for the anti-estradiol antibody 57-2 were constructed by comparative model building. Estradiol and analogs were docked into the combining site and mol. dynamics simulation was used to further refine this area of the protein. Cross-reactivities measured against 36 steroid analogs were used to help in the docking process and to evaluate the models. The roles of a no. of residues were assessed by characterization of cross-reactivity mutants obtained from a phage display library. The cross-reactivity data and the results obsd. for mutants are explained by the structural model, in which the estradiol D-ring inserts deeply into the binding site and interacts with the antibody through at least one specific hydrogen bond. The binding data strongly suggest that this hydrogen bond connects the estradiol 17-hydroxyl group with the side chain of Gln H35. As expected for the binding of a small arom. mol., the antibody binding site contains many arom. residues, e.g. Trp H50, H95 and L96 and Tyr L32, L49 and Phe L91.

IT **362-07-2**, 2-Hydroxyestradiol 2-methyl ether
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(monoclonal antibody 57-2 to estradiol cross-reactivity with)

RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)



Absolute stereochemistry.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 201 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:212448 HCAPLUS
DOCUMENT NUMBER: 128:279092
TITLE: Effects of 17.beta.-estradiol and its catechol metabolites on the contractility of human uterine artery: in vitro experiments
AUTHOR(S): Heinle, H.; Orth, N.; Neeser, E.; Lippert, T. H.
CORPORATE SOURCE: Physiological Institute I, University of Tubingen, Tubingen, 72076, Germany
SOURCE: Sex Steroids and the Cardiovascular System, Proceedings of the Interdisciplinary Workshop, 1st, Tuebingen, Oct., 1996 (1998), Meeting Date 1996, 75-84. Editor(s): Lippert, Theodore H.; Mueck, Alfred O.; Ginsburg, Jean. Parthenon Publishing: Carnforth, UK.
CODEN: 65VNAH
DOCUMENT TYPE: Conference
LANGUAGE: English

AB There is growing interest in the non-genomic effects of 17.beta.-estradiol and its metabolites on the vasculature. To study the direct effects on contractility, human uterine arteries, obtained from patients after hysterectomy, were used for the expts. Arterial rings were mounted in a measuring chamber which allowed the continuous registration of vascular wall forces. Contractions were induced by the application of KCl, serotonin and phenylephrine, resp. 17.beta.-Estradiol and the two catecholestrogen metabolites, 2-methoxyestradiol and 2-methoxyestrone, were tested either directly by administration during stimulation of contraction or after preincubation for 30 min and 22 h, resp., prior to stimulation. It could be shown for the first time that catechol metabolites of estradiol develop direct arterial relaxing effects. This action seems to be time-dependent, since direct addn. to the vessel during the stimulation of contraction had little effect, whereas after preincubation all the test substances revealed effects on contraction amplitude and velocity of force development. The relaxing or contraction-inhibiting effect can be attributed to an inhibition of the signaling mechanisms which regulate smooth muscle contraction. In different tests a relaxing mechanism by endothelium-dependent NO release could be excluded, since addn. of acetylcholine to uterine arteries did not provoke endothelium-derived relaxing factor (EDRF)-mediated relaxation.

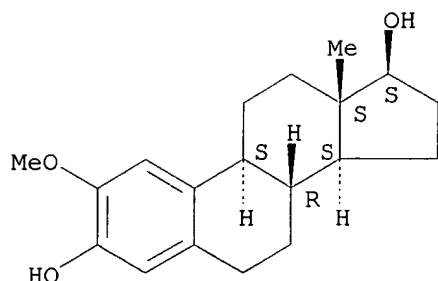
IT 362-07-2, 2-Methoxyestradiol
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effects of 17.beta.-estradiol and its catechol metabolites on the contractility of human uterine artery in vitro)

RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

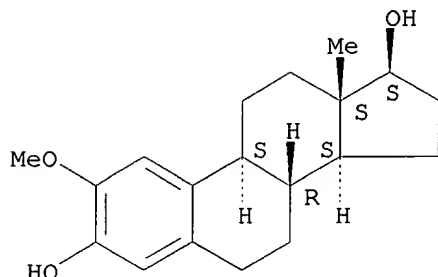
L11 ANSWER 202 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1998:212446 HCAPLUS
 DOCUMENT NUMBER: 128:279090
 TITLE: In vitro evaluations of the effects of sex steroids on the vasculature
 AUTHOR(S): Seeger, H.; Mueck, A. O.; Lippert, T. H.
 CORPORATE SOURCE: Section of Clinical Pharmacology, Department of Obstetrics and Gynecology, University of Tubingen, Tubingen, 72076, Germany
 SOURCE: Sex Steroids and the Cardiovascular System, Proceedings of the Interdisciplinary Workshop, 1st, Tuebingen, Oct., 1996 (1998), Meeting Date 1996, 45-55. Editor(s): Lippert, Theodore H.; Mueck, Alfred O.; Ginsburg, Jean. Parthenon Publishing: Carnforth, UK.
 CODEN: 65VNAH
 DOCUMENT TYPE: Conference
 LANGUAGE: English

AB The effect of 17.β-estradiol on the prodn. of the vasoactive substances nitric oxide and prostacyclin was examd. in in vitro tests on human vascular cells. No distinct effect of 17.β-estradiol alone could be obsd. The increase of prostacyclin synthesis elicited by the vasoconstrictor endothelin-1, however, was increased significantly by the addn. of 17.β-estradiol. In further expts. the ability of different sex steroids to inhibit calcium influx in human vascular muscle cells was tested. The strongest calcium antagonistic effect was shown by 17.β-estradiol. Progesterone and different progestins did not alter the calcium influx. In combination with 17.β-estradiol only the progestin norethisterone reduced the calcium antagonistic effect of 17.β-estradiol but only at high concns. Since oxidized low-d. lipoprotein (LDL) plays a significant role in the development of arteriosclerosis, the influence of 17.β-estradiol, as well as its main metabolites, and progestins on LDL oxidn. was investigated. The A-ring metabolites of 17.β-estradiol had a greater inhibitory effect on LDL oxidn. than the parent substance and the D-ring metabolites. The progestins did not show any antioxidative property either alone or in combination with 17.β-estradiol.

IT 362-07-2, 2-Methoxyestradiol
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (in vitro evaluations of the effects of sex steroids on the vasculature)

RN 362-07-2 HCAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 203 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:168790 HCAPLUS
DOCUMENT NUMBER: 128:281273
TITLE: Differential expression of CYP1A1 and CYP1B1 in human breast epithelial cells and breast tumor cells
AUTHOR(S): Spink, David C.; Spink, Barbara C.; Cao, Joan Q.; DePasquale, Joseph A.; Pentecost, Brian T.; Fasco, Michael J.; Li, Ying; Sutter, Thomas R.
CORPORATE SOURCE: New York State Department of Health, Wadsworth Center, Albany, NY, 12201-0509, USA
SOURCE: Carcinogenesis (1998), 19(2), 291-298
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human cytochromes P 450 1A1 (CYP1A1) and P 450 1B1 (CYP1B1) catalyze the metabolic activation of a no. of procarcinogens and the hydroxylation of 17.beta.-estradiol (E2) at the C-2 and C-4 positions, resp. The arom. hydrocarbon receptor (AhR) agonist 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) has a marked effect on estrogen metab. in MCF-7 breast-tumor cells by induction of these two enzymes. To investigate whether induction of CYP1A1 and CYP1B1 by AhR agonists and the assocd. increase in E2 metab. are common to all breast epithelial cells and breast-tumor cells, we detd. the effects of TCDD on E2 metab., and CYP1A1 and CYP1B1 mRNA levels in a series of non-tumor-derived breast epithelial (184A1 and MCF-10A) and breast-tumor (MCF-7, T-47D, ZR-75-1, BT-20, MDA-MB-157, MDA-MB-231 and MDA-MB-436) cell lines. In 184A1 cells, which did not express detectable estrogen receptor (ER) .alpha. mRNA, CYP1A1 mRNA and activity were induced by TCDD, and enhanced E2 metab. in TCDD-treated cells was predominantly E2 2-hydroxylation. In MCF-10A, MCF-7, T-47D, ZR-75-1 and BT-20 cells, which expressed varying levels of ER.alpha. mRNA, both CYP1A1 and CYP1B1 mRNA levels and rates of both E2 2- and 4-hydroxylation were highly elevated following exposure to TCDD. In MDA-MB-157, MDA-MB-231 and MDA-MB-436 cells, which did not express detectable ER.alpha. mRNA and generally displayed fibroblastic or mesenchymal rather than epithelial morphol., CYP1B1 induction was favored, and the rate of E2 4-hydroxylation exceeded

that of 2-hydroxylation in TCDD-treated cells. These results show that breast epithelial cells and tumor cells vary widely with regard to AhR-mediated CYP1A1 and CYP1B1 induction, suggesting that factors in addn. to the AhR regulate CYP1A1 and CYP1B1 gene expression. In these cell lines, significant CYP1A1 inducibility was restricted to cultures displaying epithelial morphol., whereas CYP1B1 inducibility was obsd. in cells of both epithelial and mesenchymal morphol.

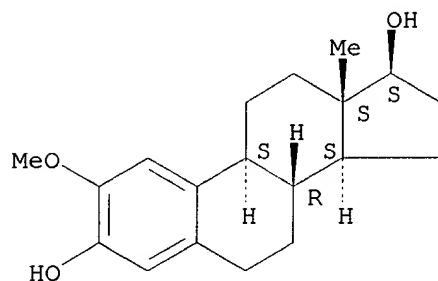
IT 362-07-2, 2-Methoxyestradiol

RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(differential expression of CYP1A1 and CYP1B1 in human breast epithelial cells and breast tumor cells)

RN 362-07-2 HCAPLUS

CN Estr-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 204 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1998:99597 HCAPLUS

DOCUMENT NUMBER: 128:180572

TITLE: Polyethylene glycol (PEG) as phase transfer catalyst for improvement of nucleophilic substitution on ring A of bromoestrogen to methoxyestrogen

AUTHOR(S): Li, Zhiliang; Xiao, Min; Liang, Benxi; Sakai, M.; Muramatsu, Y.

CORPORATE SOURCE: College of Chemistry and Chemical Engineering, Hunan Univ., Changsha, 410082, Peop. Rep. China

SOURCE: Hunan Daxue Xuebao, Ziran Kexueban (1997), 24(4), 40-43

CODEN: HDAXE3; ISSN: 1000-2472

PUBLISHER: Hunan Daxue Xuebao Bianjibu

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

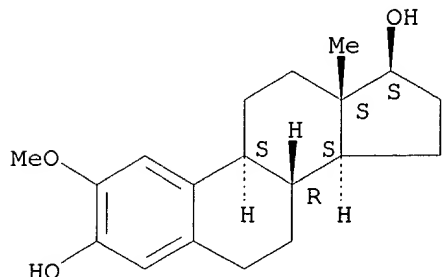
AB The effects of the type and content of reagent, solvent type, PEG content, reaction temp. and time on the yield of the reaction were discussed. The yields were 66.7 and 70.3 for 2-methoxyestrogen and 4-methoxyestrogen, resp.

IT 362-07-2P

RL: SPN (Synthetic preparation); PREP (Preparation)
(PEG as phase transfer catalyst for improvement of nucleophilic substitution on ring A of bromoestrogen to methoxyestrogen)

RN 362-07-2 HCAPLUS
 CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 205 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1998:98349 HCAPLUS
 DOCUMENT NUMBER: 128:176478
 TITLE: 2-Methoxyestradiol facilitation of p53-induced apoptosis in cancer cells
 INVENTOR(S): Mukhopadhyay, Tapas; Roth, Jack A.
 PATENT ASSIGNEE(S): Board of Regents, the University of Texas System, USA; Mukhopadhyay, Tapas; Roth, Jack A.
 SOURCE: PCT Int. Appl., 78 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9804291	A1	19980205	WO 1997-US12998	19970724
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
US 5958892	A	19990928	US 1996-688613	19960730
AU 9737383	A1	19980220	AU 1997-37383	19970724
AU 723401	B2	20000824		
EP 921821	A1	19990616	EP 1997-934286	19970724
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
JP 2000517299	T2	20001226	JP 1998-508981	19970724
US 6410029	B1	20020625	US 1999-351191	19990709
US 2003099614	A1	20030529	US 2002-180893	20020625
PRIORITY APPLN. INFO.:			US 1996-688613 A2	19960730
			WO 1997-US12998 W	19970724
			US 1999-351191 A1	19990709

AB The present invention details methods for the treatment of cancer. In particular, it concerns the induction of apoptosis of cancer cells following treatment with methoxyestradiol. 2-Methoxyestradiol (2-MeOE2) increases wild-type p53 levels in a human non-small lung cancer cell lines assocd. with accumulation of cyclin dependent kinase inhibitor p21WAF1/CIP1. Significant apoptotic cell death occurred after the drug treatment. Thus, 2-MeOE2 facilitates induction of p53-mediated apoptosis. The p53 may be an endogenous or exogenous protein. It is one of the goals of the present invention to provide improved methods for the treatment of cancers comprising administration a p53 gene in conjunction with an agent that increases the level of p53 in the cells.

IT 362-07-2, 2-Methoxyestradiol

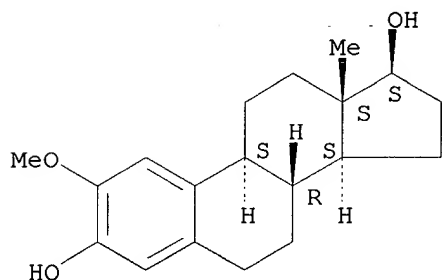
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(2-methoxyestradiol facilitation of p53-induced apoptosis in cancer cells)

RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 206 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1998:91974 HCAPLUS
 DOCUMENT NUMBER: 128:188743
 TITLE: 17.beta.-Estradiol, its metabolites, and progesterone inhibit cardiac fibroblast growth
 AUTHOR(S): Dubey, Raghvendra K.; Gillespie, Delbert G.; Jackson, Edwin K.; Keller, Paul J.
 CORPORATE SOURCE: Center for Clinical Pharmacology, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, 15213-2582, USA
 SOURCE: Hypertension (1998), 31(1, Pt. 2), 522-528
 CODEN: HPRTDN; ISSN: 0194-911X
 PUBLISHER: Williams & Wilkins
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB 17.beta.-Estradiol and progesterone, but not 17.alpha.-estradiol, estrone, or estriol, inhibited 2.5% fetal calf serum (FCS)-induced proliferation (DNA synthesis and cell no.) and collagen synthesis (3H-proline incorporation) in a concn.-dependent manner and to a similar extent in

male and female cardiac fibroblasts (CFs). Compared to 17.β.-estradiol, its metabolites 2-hydroxyestradiol and 2-methoxyestradiol were more potent in inhibiting FCS-induced DNA synthesis, collagen synthesis, and cell proliferation. The inhibitory effects of 17.β.-estradiol and its metabolites were enhanced in presence of progesterone and 4-hydroxytamoxifen (high-affinity estrogen receptor ligand). Moreover, like estrogens, the dietary phytoestrogens biochanin A and daidzein inhibited FCS-induced growth of CFs. In conclusion, 17.β.-estradiol, its metabolites, and progesterone inhibit CF growth in a gender-independent fashion.

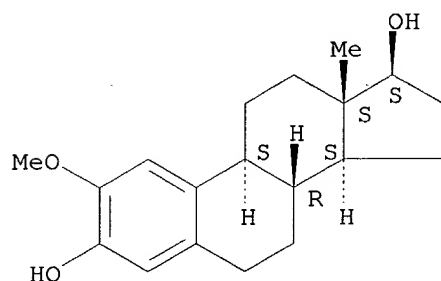
IT 362-07-2, 2-Methoxyestradiol

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(estradiol, its metabolites, and progesterone inhibit cardiac fibroblast growth)

RN 362-07-2 HCAPLUS

CN Estradiol, 1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.β.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 207 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1998:34691 HCAPLUS

DOCUMENT NUMBER: 128:136620

TITLE: Estradiol induces C-type natriuretic peptide gene expression in mouse uterus

AUTHOR(S): Acuff, Cory G.; Huang, Huaming; Steinhilber, Mark E.

CORPORATE SOURCE: Dep. of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, 78284-7756, USA

SOURCE: American Journal of Physiology (1997), 273(6, Pt. 2), H2672-H2677

CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Previous expts. have demonstrated that C-type natriuretic peptide (CNP) expression in the uterus varies during the estrus cycle with maximal expression at proestrus. The present study was designed to det. whether exogenous steroid hormones regulate uterine CNP expression in ovariectomized mice. Estradiol increased significantly (3-fold) uterine immunoreactive CNP (irCNP) rapidly and dose dependently in ovariectomized

mice as measured by RIA. Other steroids produced either no significant change (testosterone, 1 mg; 2-methoxyestradiol, 1 .mu.g) or weak induction (estriol, 1 .mu.g) from vehicle controls. Progesterone (1 mg) significantly attenuated the estrogen-stimulated irCNP response by 50% when injected 30 min before estrogen (1 .mu.g) in estrogen-primed ovariectomized mice. Estrogen-stimulated increases in uterine CNP transcripts detected by RNase protection analyses were blocked by actinomycin D (160 .mu.g) or ICI-164,384 (20 .mu.g), a specific nuclear estrogen receptor antagonist. These results indicate to stimulate uterine CNP transcription and that progesterone neg. regulates estrogen-stimulated CNP expression.

IT 362-07-2, 2-Methoxyestradiol

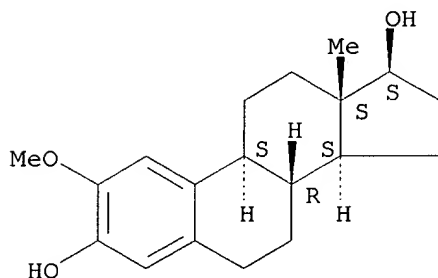
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(estradiol induces C-type natriuretic peptide gene expression in mouse uterus)

RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 208 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1998:10247 HCAPLUS

DOCUMENT NUMBER: 128:97804

TITLE: The mammalian metabolite, 2-methoxyestradiol, affects P53 levels and apoptosis induction in transformed cells but not in normal cells

AUTHOR(S): Seegers, Johanna C.; Lottering, Mona-Liza; Grobler, Christina J. S.; van Papendorp, Dirk H.; Habbersett, Robert C.; Shou, Yulin; Lehnert, Bruce E.

CORPORATE SOURCE: Department of Physiology, University of Pretoria, Pretoria, S. Afr.

SOURCE: Journal of Steroid Biochemistry and Molecular Biology (1997), 62(4), 253-267

CODEN: JSBBEZ; ISSN: 0960-0760

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The endogenous metabolite, 2-methoxyestradiol (2ME), is an inhibitor of tubulin polymn. and is therefore toxic to dividing fast-growing tumor cells. Transformed cells are not equally susceptible to the effects of

2ME. In this study the effects of 1-2 .mu.M doses of 2ME on cell cycle progression, apoptosis induction and on p53 levels were evaluated using flow cytometry in cells with different p53 status. No effect of 2ME was seen in normal human skin fibroblast strain HSF43 with wild-type (wt) p53. However, in SV40 T antigen transformed HSF43 cells (line E8T4), 2ME caused a prominent G2/M arrest, with subsequent micronuclei formation followed by apoptosis. Increased p53 levels were present in the G2/M cells. The results suggest that 2ME, being a microtubule poison, may release the bound p53 from T antigen, and that this p53 may enhance the apoptotic effects. Two lymphoblast cell lines derived from the same donor, TK6, expressing low levels of wt p53, and WTK1, expressing high levels of mutant p53, showed similar moderate responses to 2ME at 37.degree.C. The effects included enhanced apoptosis and a modest G2/M block. No increase in p53 levels was seen. However, at the permissive temp. of 30.degree.C marked increases in apoptosis and a prominent G2/M-phase block, similar to that seen in the E8T4 cells, were present in the WTK1 cells, indicating that the high levels of mutant p53 have now become functional, enhancing the apoptotic effects initiated by 2ME.

IT 362-07-2, 2-Methoxyestradiol

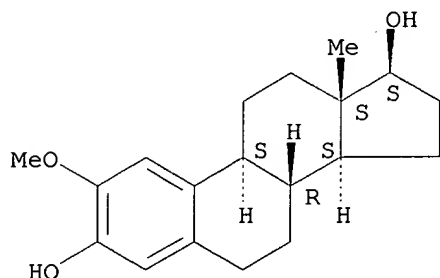
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(2-methoxyestradiol affects P53 levels and apoptosis induction in human transformed cells but not in normal cells)

RN 362-07-2 HCAPLUS

CN Estr-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 209 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1997:800058 HCAPLUS

DOCUMENT NUMBER: 128:71835

TITLE: Synergistic induction of DNA strand breakage by catechol-estrogen and nitric oxide: implications for hormonal carcinogenesis

AUTHOR(S): Yoshie, Yumiko; Ohshima, Hiroshi

CORPORATE SOURCE: Unit of Endogenous Cancer Risk Factors, International Agency for Research on Cancer, Lyon, 69372, Fr.

SOURCE: Free Radical Biology & Medicine (1997), Volume Date 1998, 24(2), 341-348

CODEN: FRBMEH; ISSN: 0891-5849

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have demonstrated that DNA strand breakage is induced synergistically when pBR322 plasmid DNA is incubated in the presence of both a nitric oxide (NO)-releasing compd. (diethylamine NONOate, etc.) and a catechol-estrogen (2- or 4-hydroxyestradiol or -hydroxyestrone). Either the NO-releasing compd. or the catechol-estrogen alone induced much fewer strand breaks. Estradiol, estrone, O-methylated catechol-estrogens, and diethylstilbestrol did not exert such DNA damaging effects. Strand breakage induced by NO plus 2- or 4-hydroxyestradiol was inhibited by carboxy-PTIO (an NO-trapping agent) and, to a lesser extent, by superoxide dismutase. Antioxidants (e.g., N-acetylcysteine, ascorbate), but not HO.scavengers, exhibited inhibitory effects. A possible mechanism for this strand breakage would be: (1) NO mediates conversion of catechol-estrogens to quinones, (2) the quinone/hydroquinone redox system produces O₂.- and (3) O₂.- reacts with NO to form peroxynitrite, which causes DNA strand breaks. Our results imply that interaction of catechol-estrogens and NO, both known to be formed in human breast and uterus, leads to prodn. of a potent oxidant(s), which could cause damage in cells and DNA, thus playing an important role in hormonal carcinogenesis.

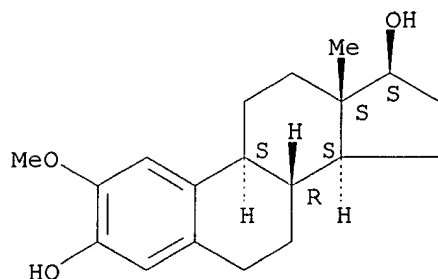
IT 362-07-2, 2-Methoxyestradiol

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(synergistic induction of DNA strand breakage by catechol-estrogen and nitric oxide in relation to hormonal carcinogenesis)

RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 210 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1997:752842 HCAPLUS

DOCUMENT NUMBER: 128:30711

TITLE: Treatment of asthma and airway diseases using steroids or steroid analogs

INVENTOR(S): Stewart, Alastair George

PATENT ASSIGNEE(S): Amrad Operations Pty. Ltd., Australia; Stewart, Alastair George

SOURCE: PCT Int. Appl., 63 pp.

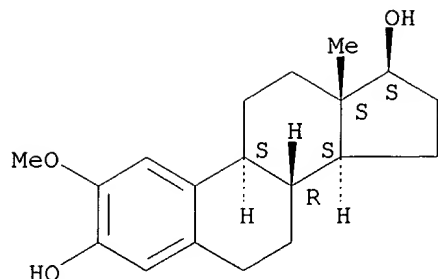
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

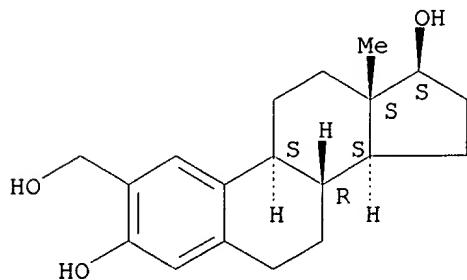
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9742958	A1	19971120	WO 1997-AU286	19970509
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9726276	A1	19971205	AU 1997-26276	19970509
AU 725048	B2	20001005		
CN 1218401	A	19990602	CN 1997-194505	19970509
EP 923376	A1	19990623	EP 1997-917945	19970509
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 5962445	A	19991005	US 1997-853528	19970509
JP 2000507923	T2	20000627	JP 1997-530434	19970509
US 6200966	B1	20010313	US 1999-330918	19990611
PRIORITY APPLN. INFO.:				
			AU 1996-9766	A 19960509
			AU 1996-9918	A 19960520
			US 1997-853528	A1 19970509
			WO 1997-AU286	W 19970509
AB	The invention relates to use of steroids or steroid analogs in the treatment of chronic and acute inflammation of the airways, particularly asthmatic conditions. It also relates to compds. and compns. which modulate airway remodelling. In a preferred embodiment, the active component inhibits inflammation and smooth muscle cell proliferation in the airway wall. It may also have a least one other activity selected from antiangiogenesis, antioxidn., and the ability to disrupt microtubule formation. In a preferred embodiment, the steroid is 2-methoxyoestradiol.			
IT	362-07-2, 2-Methoxyestradiol RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (treatment of asthma and airway diseases using steroids or steroid analogs)			
RN	362-07-2 HCAPLUS			
CN	Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)			

Absolute stereochemistry.



L11 ANSWER 435 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1963:410284 HCAPLUS
 DOCUMENT NUMBER: 59:10284
 ORIGINAL REFERENCE NO.: 59:1916c-e
 TITLE: Estrogens. V. The relation of estrogenic activity and molecular structure
 AUTHOR(S): Patton, Tad L.; Dmochowski, Leon
 CORPORATE SOURCE: Univ. of Texas M. D. Anderson Hosp., Houston
 SOURCE: Archives of Biochemistry and Biophysics (1963), 101, 181-5
 CODEN: ABBIA4; ISSN: 0003-9861
 DOCUMENT TYPE: Journal
 LANGUAGE: Unavailable
 AB cf. CA 57, 7341b. Changes in estrogenic activity in ovariectomized mice caused by substituents at positions 2 and 4 of estrone and 17.β-estradiol are reported. Both position and structure of the substituent det. the estrogenic activity of the compd. Two factors seem to have a predominating influence on estrogenic activity: a steric factor in which the phenolic OH group of an estrogen is shielded by a large group, making it difficult for the former to form H bond with a biol. important substrate; compds. with a substituent capable of forming a strong intramol. H bond with the phenolic OH group exhibit low estrogenic activity.
 IT **94440-60-5**, Estra-1,3,5(10)-triene-3,17.β.-diol, 2-(hydroxymethyl)- (prepn. and estrogenic activity of)
 RN 94440-60-5 HCAPLUS
 CN Estra-1,3,5(10)-triene-3,17-diol, 2-(hydroxymethyl)-, (17.β.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 436 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1963:34604 HCAPLUS
DOCUMENT NUMBER: 58:34604
ORIGINAL REFERENCE NO.: 58:5955e-h,5956a-b
TITLE: Estrogen metabolism in the human fetus. I. Tissue levels following the administration of 17.beta.-estradiol and estriol
AUTHOR(S): Diczfalusy, E.; Cassmer, O.; Alonso, C.; de Miquel, M.
CORPORATE SOURCE: Karolinska Hosp., Stockholm
SOURCE: Acta Endocrinologica (1961), 37, 353-75
CODEN: ACENA7; ISSN: 0001-5598
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To test a hypothesis that the human fetus actively participates in the estrogen (I) metabolism during pregnancy, I was introduced into the fetus prior to therapeutic abortions. Intravenous infusion of the mothers with as much as 100 mg. estriol (II) did not increase II in the amniotic fluid and conjugated II was increased to only a very limited extent in the fetal lungs and liver. Intraamniotic injection was very effective in introducing I into the fetus since I so injected was rapidly swallowed (and perhaps aspirated) by the fetus. Intraamniotic injection of 25 mg. 17.beta.-estradiol (III) greatly increased conjugated I, estrone (IV), II, and III in several (named) fetal organs. Conjugation was very active in the fetal lungs but the increase of conjugated I in the placenta was very limited. When II or III was injected into the amniotic fluid it was rapidly reduced to 1/2 the initial concn. after 2 hrs. and disappeared within 24 hrs. The results indicate that any existing placentoamniotic barrier is more readily penetrated by I from the fetal side than from the maternal side. Hydroxylation or methoxylation (or both) in the 2 position appears to be important in the fetal degradation of III. It has been shown that fetal liver tissue in vitro converts 2-hydroxyestradiol to 2-methoxyestradiol. The results are interpreted in relation to other reports on fetal steroid metabolism. 23 references. II. Estrogen conjugation by fetal organs in vitro and in vivo. Ibid. 516-28. The incubation of II with fetal tissue slices in vitro resulted in an increase in conjugated II for liver, lungs, adrenals, and perhaps also skeletal muscle. No such increases were found for the incubation of adult endometrial or myometrial tissues, or when fetal tissues were incubated in the absence of II. Examn. of the material formed by fetal tissue in vitro indicates that it may be II 3-sulfate. Intraamniotic injections of II or III into women in whom the fetus was previously sepd. in situ from its placental connections resulted in elevated concns. of conjugated II, III, and IV in the fetal lungs and livers. Similar injections of III raised the concns. of conjugated compds. in the intestines as well as the lungs and livers. However, under the conditions, concn. of conjugated estrone, II or III was lower than in similarly treated patients with an intact fetoplacental connection. When early (previable) fetuses were perfused with dild. blood contg. added II or III, increased concns. of II or of estrone plus III, resp., were found in the lungs, liver, intestines, and kidneys plus adrenal glands. Thus, the human fetus appeared to be an important site of I conjugation at relatively early stages of gestation. 17 references. III. Nature of the conjugated estrogen formed by the fetus. Ibid. 38, 31-49. Products of intraamniotic injection or perfusion of the compds. were detd. Fetuses treated with III formed III 3-sulfate and (indirectly) Na estrone sulfate (V) in the lungs, liver, and kidneys. The liver contained all addnl. compd., probably 2-methoxy-III. V was

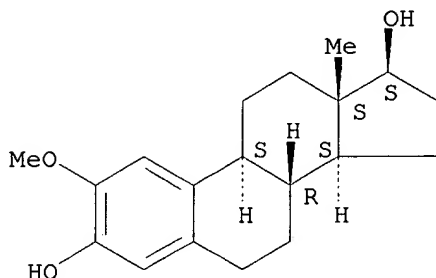
identified in exts. of lungs, liver, and kidneys of fetuses treated with II. In pooled exts. of intestines of untreated fetuses, 2 conjugated forms of II were found, probably Na II 3-sulfate and Na II-16(17?)-glucosiduronate. At least the lungs, liver, and kidneys of the human fetus can sulfurylate steroid estrogens. This change may also occur in other organs. The intestinal mucosa may be a potential site of I glucuronide formation. 20 references.

IT **362-07-2**, Estra-1,3,5(10)-triene-3,17.beta.-diol, 2-methoxy-
(as estrogen metabolite in embryo)

RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 437 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1962:457768 HCAPLUS

DOCUMENT NUMBER: 57:57768

ORIGINAL REFERENCE NO.: 57:11550c-d

TITLE: Enzymic demethylation of 2-methoxy estrogens

AUTHOR(S): Mittermayer, C.; Breuer, H.

CORPORATE SOURCE: Univ. Clin. Polyclin., Bonn, Germany

SOURCE: Naturwissenschaften (1962), 49, 328

CODEN: NATWAY; ISSN: 0028-1042

DOCUMENT TYPE: Journal

LANGUAGE: Unavailable

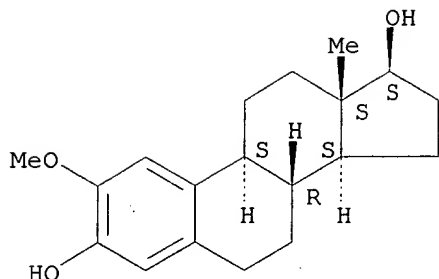
AB 2-Methoxy-17.beta.-estradiol was demethylated by microsome soln. of male Wistar rats at pH 7.4. In a 60-min. reaction time 3 phenolic compds. were detected by paper chromatography using Folin-Ciocalteu reagent. 2,17.beta.-Estradiol in 2.5% yield Was one of them.

IT **362-07-2**, Estra-1,3,5(10)-triene-3,17.beta.-diol, 2-methoxy-
(demethylation by enzymes)

RN 362-07-2 HCAPLUS

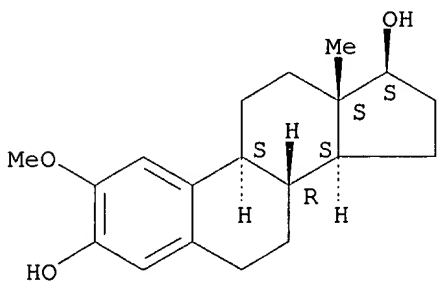
CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 438 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1962:439047 HCAPLUS
 DOCUMENT NUMBER: 57:39047
 ORIGINAL REFERENCE NO.: 57:7833d-f
 TITLE: Formation of 2-methoxy-17.β.-estradiol in human steroid-producing tissues by a transmethylation reaction
 AUTHOR(S): Axelrod, Leonard R.; Goldzieher, Joseph W.
 CORPORATE SOURCE: Southwest Found. for Res. & Educ., San Antonio, TX
 SOURCE: Endocrinology (1962), 70, 943-5
 CODEN: ENDOAO; ISSN: 0013-7227
 DOCUMENT TYPE: Journal
 LANGUAGE: Unavailable
 AB Human testis, ovary, and adrenal were incubated with 2-hydroxy-17.β.-estradiol, methionine-methyl-C14, adenosine triphosphate, and other cofactors. 2-Methoxyestrone and 2-methoxy-17.β.-estradiol were produced by gonadal tissues but only the 2nd by adrenal tissue. Testis showed the highest level of radioactivity. No compds. more polar than 2-methoxy phenolic steroids were found. Steroid-producing organs carry on transmethylation and are primary producers of urinary 2-methoxy estrogens.
 IT **362-07-2**, Estra-1,3,5(10)-triene-3,17.β.-diol, 2-methoxy- (formation of, in adrenals by transmethylation)
 RN 362-07-2 HCAPLUS
 CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.β.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 439 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1962:436526 HCAPLUS
 DOCUMENT NUMBER: 57:36526

ORIGINAL REFERENCE NO.: 57:7339i,7340a-c
TITLE: Steroids. CLXXVI. Claisen rearrangement of estrone allyl ether
AUTHOR(S): Holton, P. G.
CORPORATE SOURCE: Syntex S. A., Mex.
SOURCE: Journal of Organic Chemistry (1962), 27, 357-61
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

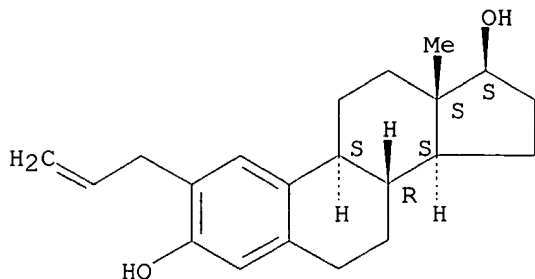
AB cf. preceding abstr. Rearrangement of estrone allyl ether (I) in refluxing PhNEt₂ gave a 3:1 mixt. of 4-allyl- (II) and 2-allylestrones (III). Each isomer was reduced to the corresponding C-allyl and C-propylestradiol. Structural assignments were made on the basis of nuclear magnetic resonance (n.m.r.), infrared, and ultraviolet spectra, and on mol. rotation relationships. Estrone treated with allyl chloride and KI gave 88% I, m. 106-7.degree.. I (22 g.) in 175 ml. PhNEt₂ refluxed 10 hrs., the soln. dild. with 2 l. Et₂O, washed with dil. acid, and the soln. evapd. and chromatographed on silica gave a mixt. of products sepd. by crystn. into 4.7 g. III, plates, m. 186-7.degree., [.alpha.]_D 152.2.degree.; benzoate, plates, m. 194-5.degree., [.alpha.]_D 119.2.degree.. Further crystn. of the rearrangement product gave 14.4 g. II, needles, m. 136-7.degree., [.alpha.]_D 115.3.degree.; benzoate m. 165-6.degree., [.alpha.]_D 84.6.degree.. NaBH₄ (0.5 g.) in 15 ml. H₂O left overnight with 0.5 g. III in 50 ml. MeOH, then neutralized with AcOH, collected, washed, and dried gave 435 mg. 2-allylestradiol (IV), m. 82-4.degree., [.alpha.]_D 88.1.degree.. II (0.5 g.) in 30 ml. MeOH reduced with 0.5 g. NaBH₄ in 15 ml. H₂O overnight gave 456 mg. 4-allylestradiol (V), m. 90-1.degree. and 140.degree., [.alpha.]_D 44.3.degree.. IV (0.7 g.) in 50 ml. alc. hydrogenated over 35 mg. PtO₂ at room temp. and pressure gave 590 mg. 2-propylestradiol, m. 89-91.degree., [.alpha.]_D 76.6.degree.. V (250 mg.) in 25 ml. alc. hydrogenated in 1 hr. over 25 ml. PtO₂ gave 193 mg. 4-propylestradiol, m. 94-4.5.degree., [.alpha.]_D 31.2.degree.. Infrared, n.m.r., and optical data for the above compds. were given.

IT 10506-67-9, Estra-1,3,5(10)-triene-3,17.beta.-diol, 2-allyl- (prepn. of)

RN 10506-67-9 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17.beta.-diol, 2-allyl- (7CI, 8CI) (CA INDEX NAME)

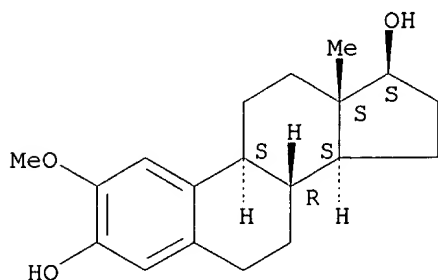
Absolute stereochemistry.



L11 ANSWER 440 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1962:431298 HCAPLUS

DOCUMENT NUMBER: 57:31298
ORIGINAL REFERENCE NO.: 57:6296h-i,6297a
TITLE: Enzymic methylation of 2-hydroxy-17.β.-estradiol by an S-adenosylmethionine-acceptor O-methyl transferase of rat liver
AUTHOR(S): Breuer, H.; Vogel, W.; Knuppen, R.
CORPORATE SOURCE: Univ. Bonn, Germany
SOURCE: Hoppe-Seyler's Zeitschrift fuer Physiologische Chemie (1962), 327, 217-24
CODEN: HSZPAZ; ISSN: 0018-4888
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB An S-adenosylmethionine catechol O-methyl transferase (I) was enriched 25-30-fold from rat liver by the method of Axelrod and Tomchick (CA 53, 2311h). After incubation of I, 2-hydroxy-17.β.-estradiol (II), S-adenosylmethionine (III), and MgCl₂ in phosphate buffer, pH 7.8, the mixt. was extd. with Et₂O-CHCl₃ (3:1 by vol.), chromatographed on paper in a formamide-chlorobenzene solvent, and quant. detns. were made with the Folin-Ciocalteu reagent. The product was identified as 2-methoxy-17.β.-estradiol (IV) on comparison with a authentic sample by chromatographic behavior, Kober reaction, H₂SO₄ reaction, m.p., ultraviolet spectrum in EtOH, and infrared spectrum in KBr. IV was not decompd. by I. The reaction has a pH optimum of 7.8 and a K_m for II of 8.7 .times. 10⁻⁴M. Estrone, 17.β.-estradiol, and estriol were not methylated.
IT **362-07-2**, Estra-1,3,5(10)-triene-3,17.β.-diol, 2-methoxy- (formation of, from 2-hydroxy-17.β.-estradiol by pyrocatechol O-methyltransferase)
RN 362-07-2 HCAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.β.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 441 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1962:10329 HCAPLUS
DOCUMENT NUMBER: 56:10329
ORIGINAL REFERENCE NO.: 56:1939g-i
TITLE: Conversion of 2-hydroxy-17.β.-estradiol to 2-hydroxy and 2-methoxy metabolites in human urine
AUTHOR(S): Axelrod, Leonard R.; Rao, P. Narasimha; Goldzieher, Joseph W.
CORPORATE SOURCE: Southwest Foundation for Research and Educ., San Antonio, TX

SOURCE: Archives of Biochemistry and Biophysics (1961), 94, 265-8
CODEN: ABBIA4; ISSN: 0003-9861

DOCUMENT TYPE: Journal

LANGUAGE: Unavailable

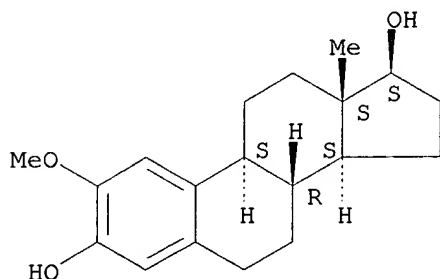
AB Intravenous infusions of 1-200 mg. 2-hydroxy-17.beta.-estradiol in plasma were administered to 4 postmenopausal women. The following urinary metabolites were definitively identified: 2-hydroxyestrone, 2-hydroxyestriol, 2-methoxyestrone, 2-methoxy-17.beta.-estradiol, and 2-methoxyestriol. The origin of the urinary estrogen Me ethers appears to be by way of transmethylation of the 2-hydroxylated compd., or as a result of further metabolism of 2-methoxyestrone.

IT **362-07-2**, Estra-1,3,5(10)-triene-3,17.beta.-diol, 2-methoxy- (in urine, after estra-1,3,5(10)-triene-2,3,17.beta.-triol administration)

RN 362-07-2 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 442 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1961:145286 HCAPLUS

DOCUMENT NUMBER: 55:145286

ORIGINAL REFERENCE NO.: 55:27586f-i

TITLE: Metabolism of 2-hydroxy-17.beta.-estradiol and 2-methoxy-17.beta.-estradiol in human and rat tissues

AUTHOR(S): Knuppen, R.; Breuer, H.; Pangels, Gerta

CORPORATE SOURCE: Poliklin., Bonn, Germany

SOURCE: Z. physiol. Chem. (1961), 324, 108-17

DOCUMENT TYPE: Journal

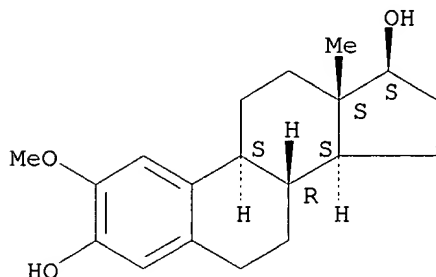
LANGUAGE: Unavailable

AB cf. CA 54, 25136c. Incubation of rat liver slices with 2-hydroxy-17.beta.-estradiol (I) and S-adenosylmethionine in phosphate buffer for 30 min. at 37.degree. yielded 2-methoxy-17.beta.-estradiol (II). II was identified after extn. with Et2O-CHCl3 mixt., by paper chromatography from C6H6-petr. ether-MeOH-H2O (33:66:80:20), RF 0.76-0.81. II m. 184-6.degree. and gives a red-violet color with Kober reagent (max. absorption at 545 m.mu.). I was converted to II by both human and rat liver, spleen, kidney, and placenta. 17.beta.-Estradiol and II are converted to nonsteroid compds. at equal rates. The monoacetate of I was prepd. from 2-benzoyl-4-nitrophenyl deriv. of I (Fishman, CA 52, 13765i) by heating 1 hr. with 20 ml. piperidine in an atm. of N, adding 200 ml. C6H6, washing with H2O, evapn., and recrystg. from C6H6-petr. ether; m.

182.5-4.5.degree.. I is prepd. by refluxing the monoacetate 3 days in a MeOH-H₂SO₄ soln., extg. with AcOH-AcOEt, recrystg. from AcOEt-petr. ether, m. 161.5-2.5.degree.. The triacetate of I is prepd. by boiling I with pyridine and (Ac)₂O, extg. with EtOH; m. 166.5-7.degree..

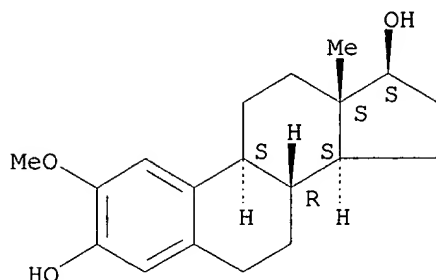
IT 362-07-2, Estradiol, 2-methoxy-
(formation of, from 2-hydroxy-17.beta.-estradiol by liver enzymes)
RN 362-07-2 HCAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



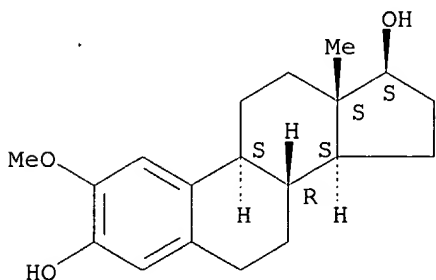
L11 ANSWER 443 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1961:65475 HCAPLUS
DOCUMENT NUMBER: 55:65475
ORIGINAL REFERENCE NO.: 55:12511c-e
TITLE: Transmethylation of 2-hydroxy estrogens by human tissue
AUTHOR(S): Axelrod, L. R.; Goldzieher, J. W.
CORPORATE SOURCE: Southwest Foundation for Research and Education, San Antonio, TX
SOURCE: Journal of Clinical Endocrinology and Metabolism (1961), 21, 211-12
CODEN: JCEMAZ; ISSN: 0021-972X
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Minced human kidney tissue was incubated in Krebs-Ringer-phosphate-glucose buffer, pH 7.4, contg. oxidized and reduced diphosphopyridine nucleotide, oxidized triphosphopyridine nucleotide, and adenosine triphosphate. To this medium was added 2-hydroxy-17.beta.-estradiol (I) and dl-methionine-methyl-C14. The lipid ext. obtained after extn. with EtOAc was chromatographed repeatedly on paper in a methylcyclohexane-propylene glycol system. The 2 radioactive zones obtained were identified as 2-methoxy-17.beta.-estradiol (II) (m. 178-80.degree.) and 2-methoxyestrone (m.176-8.degree.). Only II was produced when renal carcinoma tissue was incubated in a similar manner. Expts. with human liver and adrenal tissue failed to yield any 2-methoxy estrogens. Apparently these tissues were unable to carry out the transmethylation reaction on I.
IT 362-07-2, Estradiol, 2-methoxy-
(formation of, from transmethylation of estra-1,3,5(10)-triene-2,3,17.beta.-triol by tissue exts.)
RN 362-07-2 HCAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 444 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1961:55272 HCAPLUS
 DOCUMENT NUMBER: 55:55272
 ORIGINAL REFERENCE NO.: 55:10643a-b
 TITLE: Biogenesis of 6-hydroxyestriol and 2-methoxyestriol in rat-liver slices
 AUTHOR(S): Breuer, H.; Knuppen, R.; Schriefers, H.
 CORPORATE SOURCE: Univ. Bonn, Germany
 SOURCE: Z. physiol. Chem. (1960), 319, 136-42
 DOCUMENT TYPE: Journal
 LANGUAGE: Unavailable
 AB After incubation of the liver with estriol in Krebs phosphate soln., the products were isolated by sublimation. Identification of the products was achieved by spectrophotometry. The products were 6-hydroxyestriol (I) and 2-methoxyestriol (II). I was also obtained after incubation of 17.beta.-estradiol and 6-hydroxy-17.beta.-estradiol II was also obtained from 2-methoxy-17.beta.-estradiol.
 IT **362-07-2**, Estradiol, 2-methoxy-
 (2-methoxyestriol formation from)
 RN 362-07-2 HCAPLUS
 CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

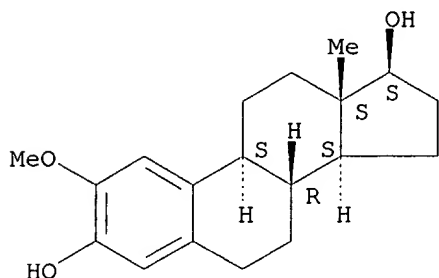
Absolute stereochemistry.



L11 ANSWER 445 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1961:28175 HCAPLUS
 DOCUMENT NUMBER: 55:28175

ORIGINAL REFERENCE NO.: 55:5608e-g
TITLE: In vitro transmethylation of 2-hydroxy-17.beta.-estradiol to 2-methoxy-17.beta.-estradiol-2-methyl-C14
AUTHOR(S): Axelrod, Leonard R.
CORPORATE SOURCE: Southwest Foundation for Research and Educ., San Antonio, TX
SOURCE: Archives of Biochemistry and Biophysics (1960), 91, 152-3
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB This report describes the formation of 2-methoxy-17.beta.-estradiol-2-methyl-C14 (I) from 2-hydroxy-17.beta.-estradiol in the presence of methionine-methyl-C14 and adenosine triphosphate (ATP) in minces of guinea pig tissues. The livers, kidneys, spleens, uteri, and quadriceps muscles were excised from mature female guinea pigs and were minced. Each tissue mince was suspended in a Krebs-Ringer phosphate-glucose buffer pH 7.4 contg. reduced and oxidized diphosphopyridine nucleotide, triphosphopyridine nucleotide, ATP, and DL-methionine-methyl-C14. 2-Hydroxy-17.beta.-estradiol was then added to the mixt. The flasks were shaken for 3 hrs. at 37.5.degree. in an atm. of 59% O2-5% CO2. The reaction was terminated by addn. of acetone, and the lipides were extd. with EtOAc. Chromatography revealed that from all tissues but liver a radioactive band occurred which upon elution, crystn., and analysis was found to be I.
IT 362-07-2, Estradiol, 2-methoxy-
(formation of, from methylation of estra-1,3,5(10)-triene-2,3,17.beta.-triol by enzymes)
RN 362-07-2 HCAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

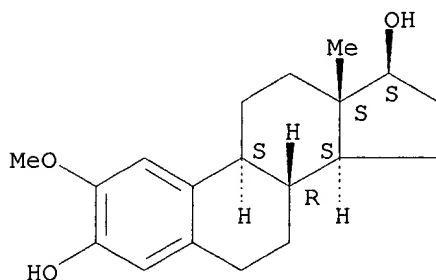
Absolute stereochemistry.



L11 ANSWER 446 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1960:130756 HCAPLUS
DOCUMENT NUMBER: 54:130756
ORIGINAL REFERENCE NO.: 54:25136c-d
TITLE: Biogenesis of 2-methoxyestradiol-17.beta. in human liver
AUTHOR(S): Breuer, H.; Knuppen, R.
CORPORATE SOURCE: Chirurg. Univ., Bonn-Venusberg, Germany
SOURCE: Naturwissenschaften (1960), 47, 280-1
CODEN: NATWAY; ISSN: 0028-1042

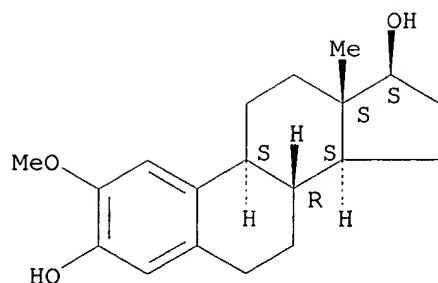
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The rate of conversion of 2-hydroxyestradiol-17.beta. (I) to 2-methoxyestradiol-17.beta. (II) was detd. when I was incubated with human liver slices in the presence of S-adenosylmethionine at 37.degree. in Krebs-Ringer-phosphate medium. The product was sepd. chromatographically (benzene/petr. ether/MeOH/H2O (33/66/80/20)) and detected with Folin-Ciocalteu's reagent. It was identical in all respects with authentic II. The results indicate that 2-methoxylation of estrogens in human liver proceeds via 2-OH intermediates, is catalyzed by a hydroxymethyltransferase, and uses S-adenosylmethionine as the CH3 donor.
IT **362-07-2**, Estradiol, 2-methoxy-
(formation of, in liver, S-adenosylmethionine and hydroxymethyltransferase in relation to)
RN 362-07-2 HCAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 447 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1960:7954 HCAPLUS
DOCUMENT NUMBER: 54:7954
ORIGINAL REFERENCE NO.: 54:1688d-e
TITLE: Demonstration of 2-methoxyestrone and of 2-methoxyestradiol in human pregnancy urine
AUTHOR(S): Frandsen, V. Aasted
CORPORATE SOURCE: Statens Seruminst., Copenhagen
SOURCE: Acta Endocrinologica (1959), 31, 603-7
CODEN: ACENA7; ISSN: 0001-5598
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In human pregnancy urine 2-methoxyestrone was identified by comparison with data in the literature for ultraviolet and infrared spectra and for partition coeffs. in different systems. The presence of 2-methoxyestradiol was demonstrated by the partition coeffs. of the substance and of its chem. derivs. with those of reduced 2-methoxyestrone.
IT **362-07-2**, Estradiol, 2-methoxy-
(detection in urine in pregnancy)
RN 362-07-2 HCAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 448 OF 448 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1958:77293 HCAPLUS
 DOCUMENT NUMBER: 52:77293
 ORIGINAL REFERENCE NO.: 52:13765i,13766a-h
 TITLE: Synthesis of 2-methoxyestrogens
 AUTHOR(S): Fishman, Jack
 CORPORATE SOURCE: Sloan-Kettering Inst. for Cancer Research, New York, NY
 SOURCE: Journal of the American Chemical Society (1958), 80, 1213-16
 CODEN: JACSAT; ISSN: 0002-7863
 DOCUMENT TYPE: Journal
 LANGUAGE: Unavailable

AB Estrone (I) (1.71 g.) added to 0.210 g. KOH in 50 cc. abs. EtOH, warmed, treated with 0.853 g. 2,5-Cl(O2N)C6H3Bz (II), refluxed 24 hrs., concd. to half the original vol., cooled, poured into N NaOH, extd. with CHCl3, and the ext. evapd. yielded 1.365 g. 3-(2-benzoyl-4-nitrophenyl) ether (III) of I, m. 240-3.degree. (MeOH), [.alpha.]26D 88.degree.; the aq. alk. soln. acidified gave 0.7 g. unchanged I. III (100 mg.) in 0.5 cc. cold. concd. H2SO4 treated after 0.5 hr. with 4 cc. glacial AcOH then with 0.5 cc. 30% H2O2, allowed to stand 0.5 hr., poured into iced H2O, filtered, the solid washed with H2O, treated with excess CH2N2 in Et2O, the resulting needles, m. 144-7.degree., refluxed 1 hr. with piperidine, dild. with C6H6, washed with dil. H2SO4, the C6H6 layer extd. with dil. aq. NaOH, and the aq. ext. acidified and extd. with CHCl3 gave a few crystals of the 13,17-secolactone, m. 204-7.degree.. 17.beta.-Estradiol (IV) (5 g.) and 0.586 g. KOH in 100 cc. EtOH refluxed 48 hrs. with 2.4 g. II, concd. to half the original vol., poured into 200 cc. N NaOH, extd. with CHCl3, the ext. dried, evapd., and the residual viscous oil dissolved in 50 cc. 1:1 petr. ether-C6H6 and chromatographed on 150 g. Al2O3 gave 90 mg. II, m. 114-16.degree., and 4.12 g. 3,17.beta.-dihydroxy-1,3,5-(10)-estratriene 3-(2-benzoyl-4-nitrophenyl) ether (V), m. 97-105.degree., [.alpha.]26D 40.degree.. V was oxidized in excellent yield to III. Further elution of the column with Et2O gave some unreacted IV. V with Ac2O and pyridine gave the acetate (VI) of V, viscous oil. VI (7.5 g.) in 4 cc. glacial AcOH treated slowly with cooling and shaking with 10 cc. cold concd. H2SO4, kept 0.5 hr. at room temp., dild. with 40 cc. glacial AcOH, treated dropwise with 10 cc. 1:1 AcOH-30% H2O2, kept 0.5 hr. at room temp., poured into iced H2O, and filtered gave 4.6 g. 2-OH deriv. (VII) of VI, m. 170-2.degree. (MeOH), [.alpha.]28.8D 21.0.degree.; 2nd crop, 1.6 g. VII (2.2 g.) in 50 cc. EtOH kept 24 hrs. at 5.degree. with excess CH2N2 in Et2O and evapd. gave 2 g. 2-MeO analog (VIII) of VII, m. 169-71.degree., [.alpha.]26D 36.degree.. VIII (432 mg.) refluxed 1 hr. in 20 cc.

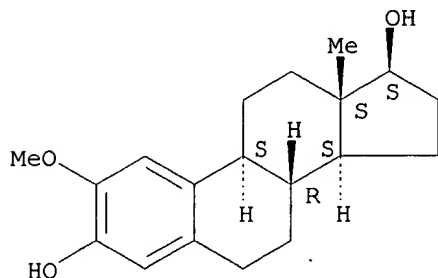
pyridine, dild. with 100 cc. C₆H₆, washed with dil. H₂SO₄ and N NaOH, evapd., and the oily residue (446 mg.) chromatographed on 16 g. Al₂O₃ yielded 180 mg. 2-methoxy-3-hydroxy-17.β.-acetoxy-1,3,5(10)-estratriene (IX), plates changing to needles, m. 194-6.degree. (C₆H₆-petr. ether), [.α.]_D²⁶ 125.degree.. IX hydrolyzed under N with 5% alc. KOH gave 2-methoxy-17.β.-estradiol (X), m. 184-6.degree. (C₆H₆). VIII (1.43 g.) in 50 cc. 6% alc. KOH refluxed 2 hrs. under N, dild. with H₂O, and extd. with C₆H₆ gave 700 mg. X, blades, m. 188-90.degree. (Me₂CO), [.α.]_D²¹ 100.degree.; diacetate of X, needles, m. 165-6.degree. (MeOH), [.α.]_D^{26.5D} 53.degree.. X partially dissolved in N NaOH and shaken with excess BzCl gave 3-monobenzoate (XI) of X, m. 195-8.degree. (MeOH), [.α.]_D^{28D} 72.degree.. VIII (203 mg.) in 40 cc. EtOH contg. 8 cc. concd. H₂SO₄ refluxed 24 hrs., dild. with H₂O, extd. with Et₂O, and the ext. worked up gave 180 mg. 2-MeO deriv. (XII) of V, m. 125-6.degree. (MeOH), [.α.]_D^{28D} 61.degree., also obtained in considerably lower yield by alk. hydrolysis of VIII at room temp. XII (290 mg.) in 40 cc. Me₂CO treated dropwise with 8N CrO₃-H₂SO₄ until an orange-brown color persisted, kept 15 min. at room temp., poured into H₂O, and extd. with CHCl₃ yielded 231 mg. 2-MeO deriv. (XIII) of I, needles, m. 204-5.degree. (MeOH), [.α.]_D^{28D} 89.degree.. XIII (240 mg.) in 20 cc. piperidine refluxed 1 hr., cooled, dild. with 100 cc. C₆H₆, washed with dil. H₂SO₄, dried, evapd., the residual oil subjected to a 99-transfer countercurrent distribution between 70% aq. MeOH and CCl₄, and the combined tubes 14-32 filtered through Al₂O₃ and crystd. from aq. MeOH gave 108 mg. 2-methoxyestrone, blades, m. 188-91.degree., giving with NaOH and BzCl the 3-monobenzoate, needles, m. 225-8.degree., which was also obtained by oxidation of XI with CrO₃.

IT **362-07-2**, Estradiol, 2-methoxy-
(and derivs.)

RN 362-07-2 HCAPLUS

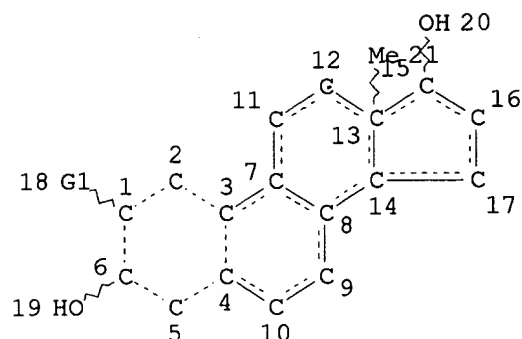
CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17.β.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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STR



N~N~N
@22 23 24

C≡C~G2
@25 26 27

Ak @

CH≡CH~G2
@28 29 30

Ak~CH≡CH2
@31 32 33

Ak~Cb~CH≡CH2
@34 35 36 37

C≡CH
@38 39

O~G2
@40 41

Ak~G3
@42 43

Ak~Cb~G3
@44 45 46

O~Ak~G3
@47 48 49

O~Ak~Cb~G3
@50 51 52 53

N~Et
@54 55

Ak~Cb
@61 62
O
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Page 1-A

60

Page 1-B

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N~C~Me
@56 57 58

Page 2-A

VAR G1=22/CN/25/28/31/34/38/40/42/44/47/50/54/56

VAR G2=60/61

VAR G3=OH/NH2/X/CF3

NODE ATTRIBUTES:

CONNECT IS E2 RC AT 2
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CONNECT IS E2 RC AT 51
 CONNECT IS E2 RC AT 52
 CONNECT IS E2 RC AT 54
 CONNECT IS E2 RC AT 56
 CONNECT IS E1 RC AT 60
 CONNECT IS E2 RC AT 61
 CONNECT IS E1 RC AT 62
 DEFAULT MLEVEL IS ATOM
 GGCAT IS UNS AT 35
 GGCAT IS UNS AT 45
 GGCAT IS UNS AT 52
 GGCAT IS UNS AT 62
 DEFAULT ECLEVEL IS LIMITED
 ECOUNT IS M6 C AT 35
 ECOUNT IS M6 C AT 45
 ECOUNT IS M6 C AT 52
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GRAPH ATTRIBUTES:

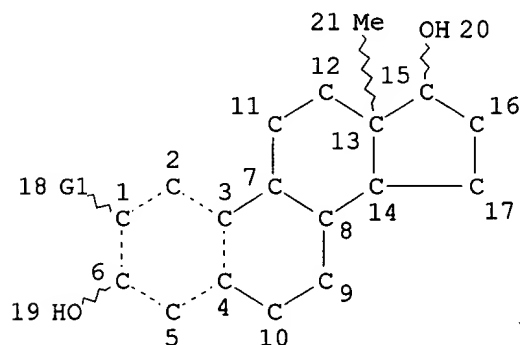
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

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L9 STR



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 @25 26 27

Ak @

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 @31 32 33

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C≡CH
 @38 39

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 @40 41

Ak~G3
 @42 43

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 @44 45 46

O~Ak~G3
 @47 48 49

O~Ak~Cb~G3
 @50 51 52 53

N~Et
 @54 55

Ak~Cb
 @61 62
 O
 |||

Page 1-B

```

      |||
      N~~C~~Me
@56 57 58

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Page 2-A

VAR G1=22/CN/25/28/31/34/38/40/42/44/47/50/54/56

VAR G2=60/61

VAR G3=OH/NH2/X/CF3

NODE ATTRIBUTES:

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CONNECT IS E2 RC AT 5

CONNECT IS E2 RC AT 9

CONNECT IS E2 RC AT 10

CONNECT IS E2 RC AT 11

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CONNECT IS E2 RC AT 35

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CONNECT IS E1 RC AT 60

CONNECT IS E2 RC AT 61

CONNECT IS E1 RC AT 62

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GGCAT IS UNS AT 45

GGCAT IS UNS AT 52

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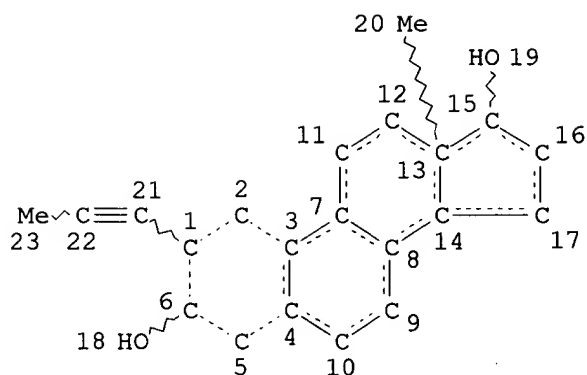
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

L10 40 SEA FILE=REGISTRY SUB=L3 SSS FUL L9

L15 STR



NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 23

STEREO ATTRIBUTES: NONE

L16 1 SEA FILE=REGISTRY SUB=L10 SSS FUL L15

L17 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L16

=> d ibib-abs-hitstr l17 1-5

L17 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:702236 HCAPLUS

DOCUMENT NUMBER: 137:353207

TITLE: The Effect of Exchanging Various Substituents at the 2-Position of 2-Methoxyestradiol on Cytotoxicity in Human Cancer Cell Cultures and Inhibition of Tubulin Polymerization

AUTHOR(S): Cushman, Mark; Mohanakrishnan, Arasambattu K.; Hollingshead, Melinda; Hamel, Ernest

CORPORATE SOURCE: Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN, 47907, USA

SOURCE: Journal of Medicinal Chemistry (2002), 45(21), 4748-4754

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A new set of estradiol derivs. bearing various substituents at the 2-position were synthesized in order to further elucidate the structural parameters assocd. with the antitubulin activity and cytotoxicity of 2-substituted estradiols. The potencies of the new compds. as inhibitors of tubulin polymn. were detd., and the cytotoxicities of the analogs in human cancer cell cultures were investigated. The substituents introduced into the 2-position of estradiol included E-3'-hydroxy-1'-propenyl, 2'-hydroxyethoxy, 3-N,N-dimethylaminoethylideneamino, 2'-

hydroxyethyleneamino, (.beta.-3,4,5-trimethoxyphenyl)ethenyl, phenylethynyl, ethynyl, 1'-propynyl, and cyano. The substituents conferring the ability to inhibit tubulin polymn. included E-3'-hydroxy-1'-propenyl, 2'-hydroxyethoxy, ethynyl, and 1'-propynyl. The remaining compds. were all inactive as inhibitors of tubulin polymn. when tested at concns. of up to 40 .mu.M. All of the compds. were cytotoxic in a panel of 55 human cancer cell cultures, and in general, the most cytotoxic compds. were also the most potent as inhibitors of tubulin polymn. 2-(1'-Propynyl)estradiol displayed significant anticancer activity in the in vivo hollow fiber animal model.

IT 192062-02-5P

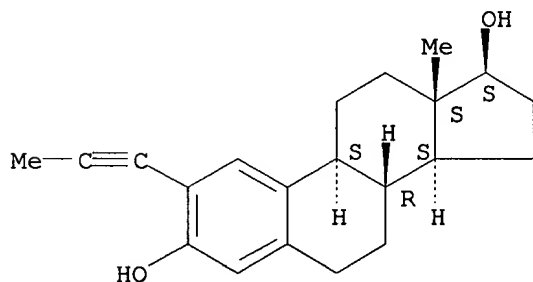
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(prepn. of estradiol derivs. with various substituents at the 2-position starting from 2-formylestradiol and evaluation of their antitumor and tubulin polymn. inhibiting activities)

RN 192062-02-5 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-(1-propynyl)-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:408687 HCAPLUS

DOCUMENT NUMBER: 137:6309

TITLE: Preparation of 2-methoxyestradiol analogs as antiangiogenic agents

INVENTOR(S): Agoston, Gregory; Shah, Jamshed H.; Hunsucker, Kimberly A.; Pribluda, Victor; Lavallee, Theresa M.; Green, Shawn J.; Herbstritt, Christopher J.; Zhan, Xiaoguo H.; Treston, Anthony

PATENT ASSIGNEE(S): Entremed, Inc., USA

SOURCE: PCT Int. Appl., 86 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002042319	A2	20020530	WO 2001-US26490	20010824

WO 2002042319 A3 20030313

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001088386 A5 20020603 AU 2001-88386 20010824

EP 1343803 A2 20030917 EP 2001-968112 20010824

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:

US 2000-253385P P 20001127

US 2000-255302P P 20001213

US 2001-278250P P 20010323

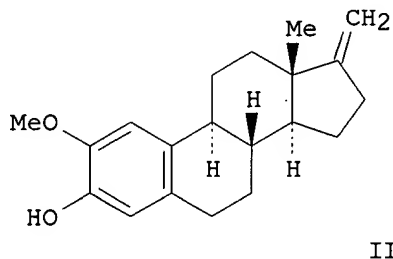
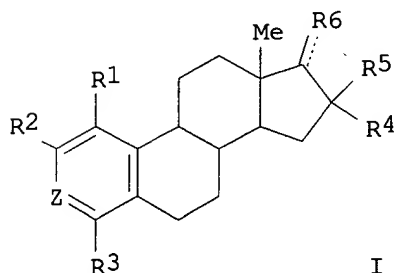
US 2001-933894 A 20010821

WO 2001-US26490 W 20010824

OTHER SOURCE(S):

MARPAT 137:6309

GI



AB 2-Methoxyestradiol analogs, such as I [R1, R3 = H, halo, CN, alkyl, OH, CH2OH, NH2, alkylamino; R2 = N3, CN, C.tplbond.CR, C=CHR, C.tplbond.CH, OR, amino; R = H, alkyl; Z = COH, COAc; dashed bond = single bond or double bond; R6 = H, OH, O, oxime, amino, alkyl, alkenyl; R4, R5 = H, alkyl, alkenyl, alkynyl], were prepd. for treating mammalian disease characterized by undesirable angiogenesis. Thus, 2-methoxyestradiol analog II was prepd. by the reaction of methyltriphenylphosphonium bromide and 2-methoxyestrone. In vitro evaluation against MDA-MB-231 breast tumor cells and HUVEC endothelial cells, II showed IC50 0.24.+-.0 and 0.19.+-.0.19 resp.

IT 192062-02-5P

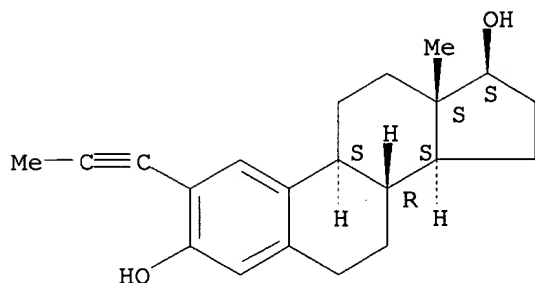
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of 2-methoxyestradiol derivs. as antiangiogenic agents)

RN 192062-02-5 HCAPLUS

CN Estradiol-1,3,5(10)-triene-3,17-diol, 2-(1-propynyl)-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L17 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:59014 HCAPLUS

DOCUMENT NUMBER: 136:288676

TITLE: Mining the National Cancer Institute's Tumor-Screening Database: Identification of Compounds with Similar Cellular Activities

AUTHOR(S): Rabow, Alfred A.; Shoemaker, Robert H.; Sausville, Edward A.; Covell, David G.

CORPORATE SOURCE: Developmental Therapeutics Program, DCTD, Science Applications International Corporation, National Cancer Institute, NIH, Frederick, MD, 21702, USA

SOURCE: Journal of Medicinal Chemistry (2002), 45(4), 818-840
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In an effort to enhance access to information available in the National Cancer Institute's (NCI) anticancer drug-screening database, a new suite of Internet accessible (<http://spheroid.ncifcrf.gov>) computational tools has been assembled for self-organizing map-based (SOM) cluster anal. and data visualization. A range of anal. questions were initially addressed to evaluate improvements in SOM cluster quality based on the data-conditioning procedures of Z-score normalization, capping, and treatment of missing data as well as completeness of drug cell-screening data. These studies established a foundation for SOM cluster anal. of the complete set of NCI's publicly available antitumor drug-screening data. This anal. identified relationships between chemotypes of screened agents and their effect on four major classes of cellular activities: mitosis, nucleic acid synthesis, membrane transport and integrity, and phosphatase- and kinase-mediated cell cycle regulation. Validations of these cellular activities, obtained from literature sources, found (i) strong evidence supporting within cluster memberships and shared cellular activity, (ii) indications of compd. selectivity between various types of cellular activity, and (iii) strengths and weaknesses of the NCI's antitumor drug screen data for assigning compds. to these classes of cellular activity. Subsequent analyses of averaged responses within these tumor panel types find a strong dependence on chemotype for coherence among cellular response patterns. The advantages of a global anal. of the complete screening data set are discussed.

IT 192062-02-5, NSC 682429

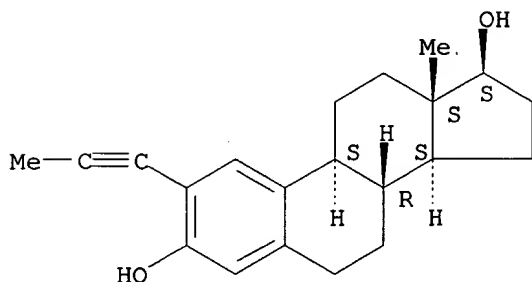
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(NSC 682429; mining National Cancer Institute's tumor-screening database and identification of compds. with similar cellular activities)

RN 192062-02-5 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-(1-propynyl)-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 116 THERE ARE 116 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:11127 HCAPLUS

DOCUMENT NUMBER: 136:64669

TITLE: Estrogenic compounds as antiangiogenic agents

INVENTOR(S): D'Amato, Robert J.; Varma, Ravi K.; Haugwitz, Rudiger G.; Cushman, Mark

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont. of U.S. Ser. No. 154,322, abandoned.

CODEN: USXXCO

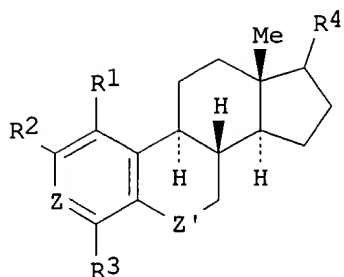
DOCUMENT TYPE: Patent

LANGUAGE: English

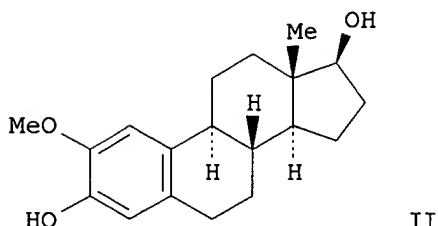
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002002294	A1	20020103	US 2001-899702	20010705
PRIORITY APPLN. INFO.:			US 1997-59916P	P 19970924
			US 1998-154322	B1 19980916
OTHER SOURCE(S):			MARPAT 136:64669	
GI				



I



II

AB 2-Methoxyestradiol derivs., such as I [R1, R3 = H, Cl, Br, I, F, CN, alkyl, OH, CH2OH, NH2, alkylamino; R2 = N3, CN, C.tplbond.CR, C=CHR, RCH=CH2, C.tplbond.CH, OR, R-R1, OR-R1 (R = alkyl, R1 = OH, NH2, Cl, Br, I, F, CF3); Z = CH, COH, CR2-OH (R2 = alkyl, aralkyl); Z' = CH2, CO, CH(OH); C=NOH, C=NOR5, CHC.tplbond.N, CHNR5R5 (R5 = H, alkyl, aralkyl)], were used for treating mammalian disease characterized by undesirable angiogenesis. Thus, 2-methoxyestradiol (II) showed inhibition of tubulin polymn. (IC50 = 3.6.+-.0.4 .mu.M), inhibition of colchicine binding to tubulin (1.9.+-.0.2 .mu.M) and antitumor activity against breast, CNS, melanoma, ovarian tumor cell assay in vitro.

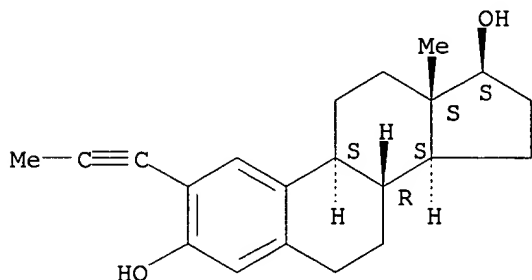
IT 192062-02-5, NSC 682429

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (estrogenic compds. as antiangiogenic agents)

RN 192062-02-5 HCAPLUS

CN Estr-1,3,5(10)-triene-3,17-diol, 2-(1-propynyl)-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L17 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1997:436019 HCAPLUS

DOCUMENT NUMBER: 127:95444

TITLE: Synthesis of Analogs of 2-Methoxyestradiol with Enhanced Inhibitory Effects on Tubulin Polymerization and Cancer Cell Growth

AUTHOR(S): Cushman, Mark; He, Hu-Ming; Katzenellenbogen, John A.; Varma, Ravi K.; Hamel, Ernest; Lin, Chii M.; Ram, Siya; Sachdeva, Yesh P.

CORPORATE SOURCE: Department of Medicinal Chemistry and Molecular Pharmacology School of Pharmacy and Pharmacal

Sciences, Purdue University, West Lafayette, IN,
47907, USA

SOURCE: Journal of Medicinal Chemistry (1997), 40(15),
2323-2334
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

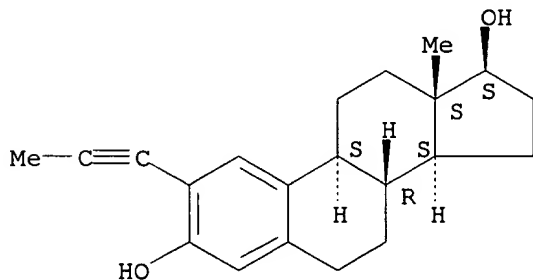
AB A new series of estradiol analogs was synthesized in an attempt to improve on the anticancer activity of 2-methoxyestradiol, a naturally occurring mammalian tubulin polymn. inhibitor. The compds. were evaluated as inhibitors of tubulin polymn. and the binding of [3H]colchicine to tubulin, as well as for in vitro cytotoxicity in human cancer cell cultures. Overall, the most potent of the new compds. were 2-(2',2',2'-trifluoroethoxy)-6-oximinoestradiol, 2-ethoxy-6-oximinoestradiol, and 2-ethoxy-6-methoximinoestradiol. These agents lacked significant affinity for the estrogen receptor. The cytotoxicities of the compds. correlated in general with their abilities to inhibit tubulin polymn., thus supporting inhibition of tubulin polymn. as the primary mechanism causing inhibition of cell growth.

IT **192062-02-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of analogs of 2-methoxyestradiol with enhanced inhibitory effects on tubulin polymn. and cancer cell growth)

RN 192062-02-5 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-(1-propynyl)-, (17.beta.)- (9CI) (CA INDEX NAME)

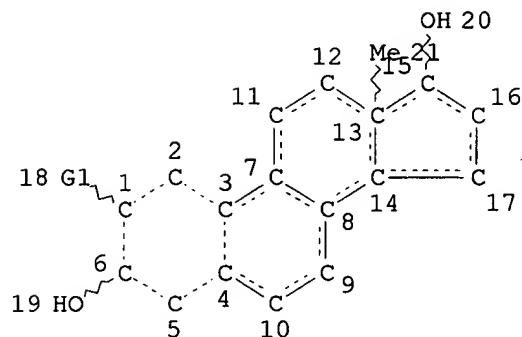
Absolute stereochemistry.



=> d que

L1

STR


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 $C \equiv C \sim G2$
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 $CH \equiv CH \sim G2$
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 $Ak \sim Cb \sim CH \equiv CH2$
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 $C \equiv CH$
 @38 39

 $O \sim G2$
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 $Ak \sim G3$
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 $O \sim Ak \sim G3$
 @47 48 49

 $O \sim Ak \sim Cb \sim G3$
 @50 51 52 53

 $N \sim Et$
 @54 55

 $Ak \sim Cb$
 @61 62
 O
 |||

Page 1-A

60

Page 1-B

 $N \sim C \sim Me$
 @56 57 58

Page 2-A

VAR G1=22/CN/25/28/31/34/38/40/42/44/47/50/54/56

VAR G2=60/61

VAR G3=OH/NH2/X/CF3

NODE ATTRIBUTES:

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CONNECT IS E2 RC AT 10

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CONNECT IS E2 RC AT 35

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CONNECT IS E2 RC AT 44

CONNECT IS E2 RC AT 45

CONNECT IS E2 RC AT 48

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CONNECT IS E2 RC AT 51
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CONNECT IS E2 RC AT 56
CONNECT IS E1 RC AT 60
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CONNECT IS E1 RC AT 62
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GGCAT IS UNS AT 45
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GGCAT IS UNS AT 62
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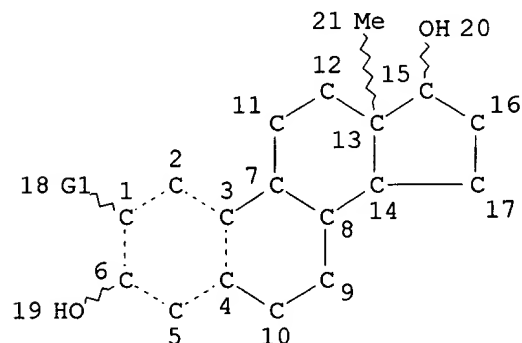
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

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L9 STR



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@25 26 27

Ak @

CH≡CH~G2
@28 29 30

Ak~CH≡CH2
@31 32 33

Ak~Cb~CH≡CH2
@34 35 36 37

C≡CH
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O~G2
@40 41

Ak~G3
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Ak~Cb~G3
@44 45 46

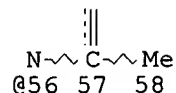
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Ak~Cb
@61 62
O
|||

Page 1-B



Page 2-A

VAR G1=22/CN/25/28/31/34/38/40/42/44/47/50/54/56

VAR G2=60/61

VAR G3=OH/NH2/X/CF3

NODE ATTRIBUTES:

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CONNECT	IS	E1	RC	AT	60
CONNECT	IS	E2	RC	AT	61
CONNECT	IS	E1	RC	AT	62
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GGCAT	IS	UNS	AT	45	
GGCAT	IS	UNS	AT	52	
GGCAT	IS	UNS	AT	62	
DEFAULT ECLEVEL IS LIMITED					
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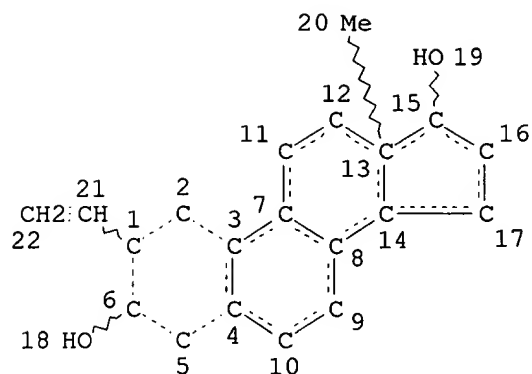
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NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

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L18 STR



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DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

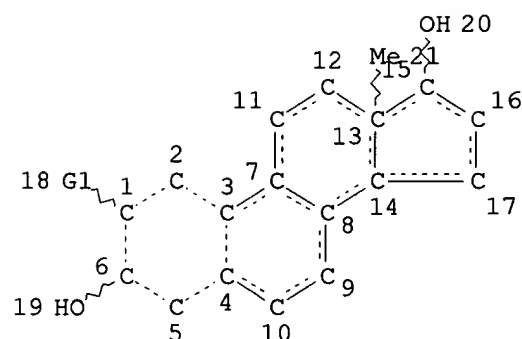
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STEREO_ATTRIBUTES: NONE

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=> d que
L1

STR



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Ak @

CH≡CH~G2
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@31 32 33

Ak~Cb~CH≡CH2
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@47 48 49

O~Ak~Cb~G3
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N~Et
@54 55

Ak~Cb
@61 62
O
||

Page 1-A

60

Page 1-B

||
N~C~Me
@56 57 58

Page 2-A

VAR G1=22/CN/25/28/31/34/38/40/42/44/47/50/54/56

VAR G2=60/61

VAR G3=OH/NH2/X/CF3

NODE ATTRIBUTES:

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CONNECT IS E2 RC AT 5

CONNECT IS E2 RC AT 10

CONNECT IS E2 RC AT 31

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CONNECT IS E2 RC AT 42

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 ECOUNT IS M6 C AT 35
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 ECOUNT IS M6 C AT 52
 ECOUNT IS M6 C AT 62

GRAPH ATTRIBUTES:

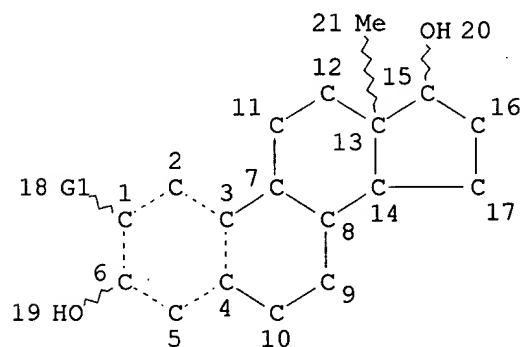
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

L3 99 SEA FILE=REGISTRY SSS FUL L1

L9 STR



$N \sim N \sim N$
 @22 23 24

$C \equiv C \sim G2$
 @25 26 27

Ak @

$CH \equiv CH \sim G2$
 @28 29 30

$Ak \sim CH \equiv CH2$
 @31 32 33

$Ak \sim Cb \sim CH \equiv CH2$
 @34 35 36 37

$C \equiv CH$
 @38 39

$O \sim G2$
 @40 41

$Ak \sim G3$
 @42 43

$Ak \sim Cb \sim G3$
 @44 45 46

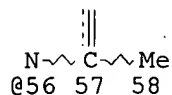
$O \sim Ak \sim G3$
 @47 48 49

$O \sim Ak \sim Cb \sim G3$
 @50 51 52 53

$N \sim Et$
 @54 55

$Ak \sim Cb$
 @61 62
 O
 ||

Page 1-B



Page 2-A

VAR G1=22/CN/25/28/31/34/38/40/42/44/47/50/54/56

VAR G2=60/61

VAR G3=OH/NH2/X/CF3

NODE ATTRIBUTES:

CONNECT IS E2 RC AT 2
 CONNECT IS E2 RC AT 5
 CONNECT IS E2 RC AT 9
 CONNECT IS E2 RC AT 10
 CONNECT IS E2 RC AT 11
 CONNECT IS E2 RC AT 12
 CONNECT IS E3 RC AT 15
 CONNECT IS E2 RC AT 16
 CONNECT IS E2 RC AT 17
 CONNECT IS E2 RC AT 31
 CONNECT IS E2 RC AT 34
 CONNECT IS E2 RC AT 35
 CONNECT IS E2 RC AT 42
 CONNECT IS E2 RC AT 44
 CONNECT IS E2 RC AT 45
 CONNECT IS E2 RC AT 48
 CONNECT IS E2 RC AT 51
 CONNECT IS E2 RC AT 52
 CONNECT IS E2 RC AT 54
 CONNECT IS E2 RC AT 56
 CONNECT IS E1 RC AT 60
 CONNECT IS E2 RC AT 61
 CONNECT IS E1 RC AT 62

DEFAULT MLEVEL IS ATOM

GGCAT IS UNS AT 35

GGCAT IS UNS AT 45

GGCAT IS UNS AT 52

GGCAT IS UNS AT 62

DEFAULT ECLEVEL IS LIMITED

ECOUNT IS M6 C AT 35

ECOUNT IS M6 C AT 45

ECOUNT IS M6 C AT 52

ECOUNT IS M6 C AT 62

GRAPH ATTRIBUTES:

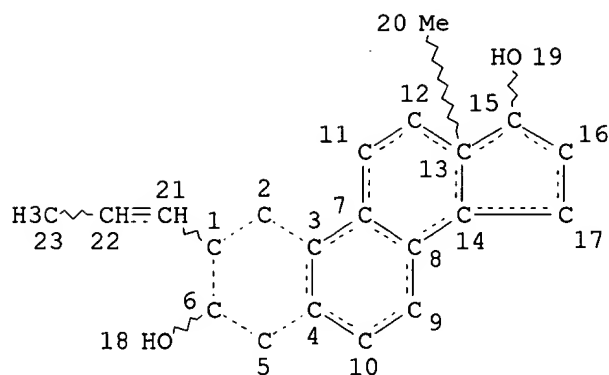
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

L10 40 SEA FILE=REGISTRY SUB=L3 SSS FUL L9

L20 STR



NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 23

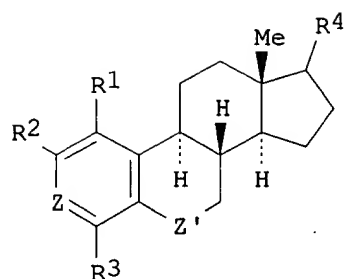
STEREO ATTRIBUTES: NONE

L21 _____ 1 SEA FILE=REGISTRY SUB=L10 SSS FUL L20
 L22 _____ 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L21

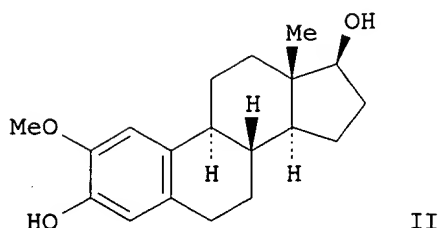
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L22 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2002:11127 HCAPLUS
 DOCUMENT NUMBER: 136:64669
 TITLE: Estrogenic compounds as antiangiogenic agents
 INVENTOR(S): D'Amato, Robert J.; Varma, Ravi K.; Haugwitz, Rudiger G.; Cushman, Mark
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont. of U.S. Ser. No. 154,322, abandoned.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002002294	A1	20020103	US 2001-899702	20010705
PRIORITY APPLN. INFO.:			US 1997-59916P	P 19970924
			US 1998-154322	B1 19980916
OTHER SOURCE(S):		MARPAT 136:64669		
GI				



I



II

AB 2-Methoxyestradiol derivs., such as I [R1, R3 = H, Cl, Br, I, F, CN, alkyl, OH, CH2OH, NH2, alkylamino; R2 = N3, CN, C.tplbond.CR, C=CHR, RCH=CH2, C.tplbond.CH, OR, R-R1, OR-R1 (R = alkyl, R1 = OH, NH2, Cl, Br, I, F, CF3); Z = CH, COH, CR2-OH (R2 = alkyl, aralkyl); Z' = CH2, CO, CH(OH); C=NOH, C=NOR5, CHC.tplbond.N, CHNR5R5 (R5 = H, alkyl, aralkyl)], were used for treating mammalian disease characterized by undesirable angiogenesis. Thus, 2-methoxyestradiol (II) showed inhibition of tubulin polymn. (IC50 = 3.6.+-.0.4 .mu.M), inhibition of colchicine binding to tubulin (1.9.+-.0.2 .mu.M) and antitumor activity against breast, CNS, melanoma, ovarian tumor cell assay in vitro.

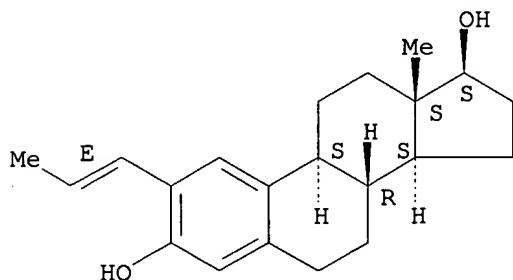
IT 165619-11-4, NSC 667047

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (estrogenic compds. as antiangiogenic agents)

RN 165619-11-4 HCAPLUS

CN Estradiol, 1,3,5(10)-triene-3,17-diol, 2-(1E)-1-propenyl-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L22 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1995:592276 HCAPLUS

DOCUMENT NUMBER: 123:112496

TITLE: Synthesis, Antitubulin and Antimitotic Activity, and Cytotoxicity of Analogs of 2-Methoxyestradiol, an Endogenous Mammalian Metabolite of Estradiol That Inhibits Tubulin Polymerization by Binding to the Colchicine Binding Site

AUTHOR(S): Cushman, Mark; He, Hu-Ming; Katzenellenbogen, John A.; Lin, Chii M.; Hamel, Ernest

CORPORATE SOURCE: Department of Medicinal Chemistry, Purdue University,
West Lafayette, IN, 47907, USA
SOURCE: Journal of Medicinal Chemistry (1995), 38(12), 2041-9
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In order to define the structural parameters assocd. with the antitubulin activity and cytotoxicity of 2-methoxyestradiol, a mammalian metabolite of estradiol, an array of analogs was synthesized and evaluated. The potencies of the new congeners as inhibitors of tubulin polymn. and colchicine binding were detd. using tubulin purified from bovine brain, and the cytotoxicities of the new compds. were studied in a variety of cancer cell cultures. Maximum antitubulin activity was obsd. in estradiols having unbranched chain substituents at the 2-position with three non-hydrogen atoms. 2-Ethoxyestradiol and 2-((E)-1-propenyl)estradiol were substantially more potent than 2-methoxyestradiol itself. The tubulin polymn. inhibitors in this series displayed significantly higher cytotoxicities in the MDA-MB-435 breast cancer cell line than in the other cell lines studied. The potencies of the analogs as cytotoxic and antimitotic agents in cancer cell cultures correlated with their potencies as inhibitors of tubulin polymn., supporting the hypothesis that inhibition of tubulin polymn. is the mechanism of the cytotoxic action of 2-methoxyestradiol and its congeners. Several of the more potent analogs were tested in an estrogen receptor binding assay, and their affinities relative to estradiol were found to be very low.

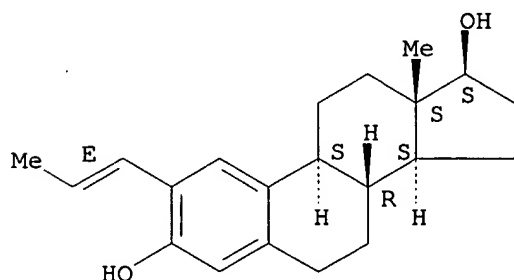
IT 165619-11-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(synthesis, antitubulin and antimitotic activity, and cytotoxicity of analogs of methoxyestradiol)

RN 165619-11-4 HCAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol, 2-(1E)-1-propenyl-, (17.beta.)- (9CI)
(CA INDEX NAME)

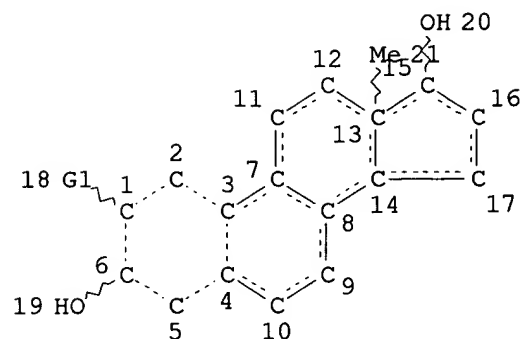
Absolute stereochemistry.
Double bond geometry as shown.



=> d que

L1

STR



$$\text{N} \sim \text{N} \sim \text{N}$$

@22 23 24

$$\text{C} \equiv \text{C} \sim \text{G2}$$

@25 26 27

Ak @

$$\text{CH} \equiv \text{CH} \sim \text{G2}$$

@28 29 30

$$\text{Ak} \sim \text{CH} \equiv \text{CH2}$$

@31 32 33

$$\text{Ak} \sim \text{Cb} \sim \text{CH} \equiv \text{CH2}$$

@34 35 36 37

$$\text{C} \equiv \text{CH}$$

@38 39

$$\text{O} \sim \text{G2}$$

@40 41

$$\text{Ak} \sim \text{G3}$$

@42 43

$$\text{Ak} \sim \text{Cb} \sim \text{G3}$$

@44 45 46

$$\text{O} \sim \text{Ak} \sim \text{G3}$$

@47 48 49

$$\text{O} \sim \text{Ak} \sim \text{Cb} \sim \text{G3}$$

@50 51 52 53

$$\text{N} \sim \text{Et}$$

@54 55

$$\text{Ak} \sim \text{Cb}$$

@61 62

O

||

Page 1-A

60

Page 1-B

$$\text{N} \sim \text{C} \sim \text{Me}$$

@56 57 58

Page 2-A

VAR G1=22/CN/25/28/31/34/38/40/42/44/47/50/54/56

VAR G2=60/61

VAR G3=OH/NH2/X/CF3

NODE ATTRIBUTES:

CONNECT IS E2 RC AT 2

CONNECT IS E2 RC AT 5

CONNECT IS E2 RC AT 10

CONNECT IS E2 RC AT 31

CONNECT IS E2 RC AT 34

CONNECT IS E2 RC AT 35

CONNECT IS E2 RC AT 42

CONNECT IS E2 RC AT 44

CONNECT IS E2 RC AT 45

CONNECT IS E2 RC AT 48

CONNECT IS E2 RC AT 51
 CONNECT IS E2 RC AT 52
 CONNECT IS E2 RC AT 54
 CONNECT IS E2 RC AT 56
 CONNECT IS E1 RC AT 60
 CONNECT IS E2 RC AT 61
 CONNECT IS E1 RC AT 62
 DEFAULT MLEVEL IS ATOM
 GGCAT IS UNS AT 35
 GGCAT IS UNS AT 45
 GGCAT IS UNS AT 52
 GGCAT IS UNS AT 62
 DEFAULT ECLEVEL IS LIMITED
 ECOUNT IS M6 C AT 35
 ECOUNT IS M6 C AT 45
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GRAPH ATTRIBUTES:

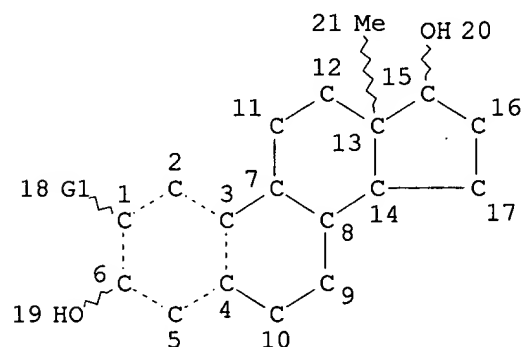
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

L3 99 SEA FILE=REGISTRY SSS FUL L1

L9 STR



$N \sim N \sim N$
 @22 23 24

$C \equiv C \sim G2$
 @25 26 27

Ak @

$CH \equiv CH \sim G2$
 @28 29 30

$Ak \sim CH \equiv CH2$
 @31 32 33

$Ak \sim Cb \sim CH \equiv CH2$
 @34 35 36 37

$C \equiv CH$
 @38 39

$O \sim G2$
 @40 41

$Ak \sim G3$
 @42 43

$Ak \sim Cb \sim G3$
 @44 45 46


$O \sim Ak \sim G3$
 @47 48 49

$O \sim Ak \sim Cb \sim G3$
 @50 51 52 53

$N \sim Et$
 @54 55

$Ak \sim Cb$
 @61 62
 O
 ||

Page 1-B



N~C~Me
@56 57 58

Page 2-A

VAR G1=22/CN/25/28/31/34/38/40/42/44/47/50/54/56

VAR G2=60/61

VAR G3=OH/NH2/X/CF3

NODE ATTRIBUTES:

CONNECT IS E2 RC AT 2

CONNECT IS E2 RC AT 5

CONNECT IS E2 RC AT 9

CONNECT IS E2 RC AT 10

CONNECT IS E2 RC AT 11

CONNECT IS E2 RC AT 12

CONNECT IS E3 RC AT 15

CONNECT IS E2 RC AT 16

CONNECT IS E2 RC AT 17

CONNECT IS E2 RC AT 31

CONNECT IS E2 RC AT 34

CONNECT IS E2 RC AT 35

CONNECT IS E2 RC AT 42

CONNECT IS E2 RC AT 44

CONNECT IS E2 RC AT 45

CONNECT IS E2 RC AT 48

CONNECT IS E2 RC AT 51

CONNECT IS E2 RC AT 52

CONNECT IS E2 RC AT 54

CONNECT IS E2 RC AT 56

CONNECT IS E1 RC AT 60

CONNECT IS E2 RC AT 61

CONNECT IS E1 RC AT 62

DEFAULT MLEVEL IS ATOM

GGCAT IS UNS AT 35

GGCAT IS UNS AT 45

GGCAT IS UNS AT 52

GGCAT IS UNS AT 62

DEFAULT ECLEVEL IS LIMITED

ECOUNT IS M6 C AT 35

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ECOUNT IS M6 C AT 52

ECOUNT IS M6 C AT 62

GRAPH ATTRIBUTES:

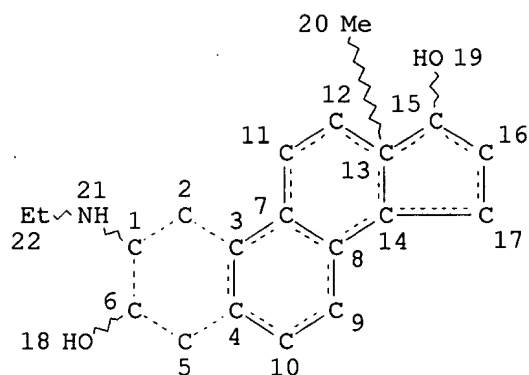
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

L10 40 SEA FILE=REGISTRY SUB=L3 SSS FUL L9

L23 STR



NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE

L24 1 SEA FILE=REGISTRY SUB=L10 SSS FUL L23
 L25 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L24

L25 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2002:59014 HCAPLUS
 DOCUMENT NUMBER: 136:288676
 TITLE: Mining the National Cancer Institute's Tumor-Screening
 Database: Identification of Compounds with Similar
 Cellular Activities
 AUTHOR(S): Rabow, Alfred A.; Shoemaker, Robert H.; Sausville,
 Edward A.; Covell, David G.
 CORPORATE SOURCE: Developmental Therapeutics Program, DCTD, Science
 Applications International Corporation, National
 Cancer Institute, NIH, Frederick, MD, 21702, USA
 SOURCE: Journal of Medicinal Chemistry (2002), 45(4), 818-840
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB In an effort to enhance access to information available in the National
 Cancer Institute's (NCI) anticancer drug-screening database, a new suite
 of Internet accessible (<http://spheroid.ncifcrf.gov>) computational tools
 has been assembled for self-organizing map-based (SOM) cluster anal. and
 data visualization. A range of anal. questions were initially addressed
 to evaluate improvements in SOM cluster quality based on the
 data-conditioning procedures of Z-score normalization, capping, and
 treatment of missing data as well as completeness of drug cell-screening
 data. These studies established a foundation for SOM cluster anal. of the
 complete set of NCI's publicly available antitumor drug-screening data.
 This anal. identified relationships between chemotypes of screened agents

and their effect on four major classes of cellular activities: mitosis, nucleic acid synthesis, membrane transport and integrity, and phosphatase- and kinase-mediated cell cycle regulation. Validations of these cellular activities, obtained from literature sources, found (i) strong evidence supporting within cluster memberships and shared cellular activity, (ii) indications of compd. selectivity between various types of cellular activity, and (iii) strengths and weaknesses of the NCI's antitumor drug screen data for assigning compds. to these classes of cellular activity. Subsequent analyses of averaged responses within these tumor panel types find a strong dependence on chemotype for coherence among cellular response patterns. The advantages of a global anal. of the complete screening data set are discussed.

IT 165619-23-8, NSC 673652

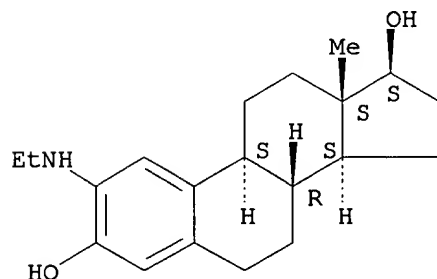
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(NSC 673652; mining National Cancer Institute's tumor-screening database and identification of compds. with similar cellular activities)

RN 165619-23-8 HCAPLUS

CN Estr-1,3,5(10)-triene-3,17-diol, 2-(ethylamino)-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 116 THERE ARE 116 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:11127 HCAPLUS

DOCUMENT NUMBER: 136:64669

TITLE: Estrogenic compounds as antiangiogenic agents

INVENTOR(S): D'Amato, Robert J.; Varma, Ravi K.; Haugwitz, Rudiger G.; Cushman, Mark

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont. of U.S. Ser. No. 154,322, abandoned.

CODEN: USXXCO

DOCUMENT TYPE: Patent

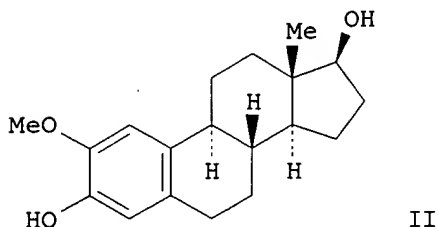
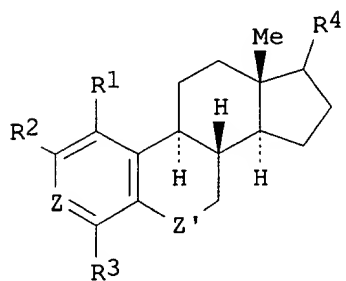
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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US 2002002294 A1 20020103 US 2001-899702 20010705
 PRIORITY APPLN. INFO.: US 1997-59916P P 19970924
 US 1998-154322 B1 19980916
 OTHER SOURCE(S): MARPAT 136:64669
 GI



AB 2-Methoxyestradiol derivs., such as I [R1, R3 = H, Cl, Br, I, F, CN, alkyl, OH, CH2OH, NH2, alkylamino; R2 = N3, CN, C.tplbond.CR, C=CHR, RCH=CH2, C.tplbond.CH, OR, R-R1, OR-R1 (R = alkyl, R1 = OH, NH2, Cl, Br, I, F, CF3); Z = CH, COH, CR2-OH (R2 = alkyl, aralkyl); Z' = CH2, CO, CH(OH); C=NOH, C=NOR5, CHC.tplbond.N, CHNR5R5 (R5 = H, alkyl, aralkyl)], were used for treating mammalian disease characterized by undesirable angiogenesis. Thus, 2-methoxyestradiol (II) showed inhibition of tubulin polymn. (IC50 = 3.6.+-0.4 .mu.M), inhibition of colchicine binding to tubulin (1.9.+-0.2 .mu.M) and antitumor activity against breast, CNS, melanoma, ovarian tumor cell assay in vitro.

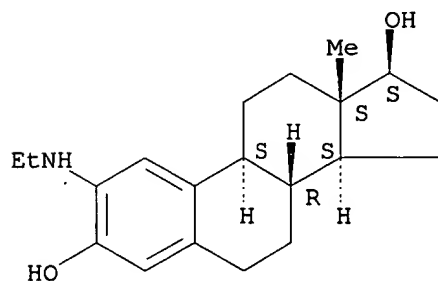
IT **165619-23-8**, NSC 673652

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (estrogenic compds. as antiangiogenic agents)

RN 165619-23-8 HCAPLUS

CN Estradiol, 1,3,5(10)-triene-3,17-diol, 2-(ethylamino)-, (17.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1995:592276 HCAPLUS

DOCUMENT NUMBER: 123:112496

TITLE: Synthesis, Antitubulin and Antimitotic Activity, and

Cytotoxicity of Analogs of 2-Methoxyestradiol, an
Endogenous Mammalian Metabolite of Estradiol That
Inhibits Tubulin Polymerization by Binding to the
Colchicine Binding Site

AUTHOR(S): Cushman, Mark; He, Hu-Ming; Katzenellenbogen, John A.;
Lin, Chii M.; Hamel, Ernest
CORPORATE SOURCE: Department of Medicinal Chemistry, Purdue University,
West Lafayette, IN, 47907, USA
SOURCE: Journal of Medicinal Chemistry (1995), 38(12), 2041-9
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In order to define the structural parameters assocd. with the antitubulin activity and cytotoxicity of 2-methoxyestradiol, a mammalian metabolite of estradiol, an array of analogs was synthesized and evaluated. The potencies of the new congeners as inhibitors of tubulin polymn. and colchicine binding were detd. using tubulin purified from bovine brain, and the cytotoxicities of the new compds. were studied in a variety of cancer cell cultures. Maximum antitubulin activity was obsd. in estradiols having unbranched chain substituents at the 2-position with three non-hydrogen atoms. 2-Ethoxyestradiol and 2-((E)-1-propenyl)estradiol were substantially more potent than 2-methoxyestradiol itself. The tubulin polymn. inhibitors in this series displayed significantly higher cytotoxicities in the MDA-MB-435 breast cancer cell line than in the other cell lines studied. The potencies of the analogs as cytotoxic and antimitotic agents in cancer cell cultures correlated with their potencies as inhibitors of tubulin polymn., supporting the hypothesis that inhibition of tubulin polymn. is the mechanism of the cytotoxic action of 2-methoxyestradiol and its congeners. Several of the more potent analogs were tested in an estrogen receptor binding assay, and their affinities relative to estradiol were found to be very low.

IT 165619-23-8P

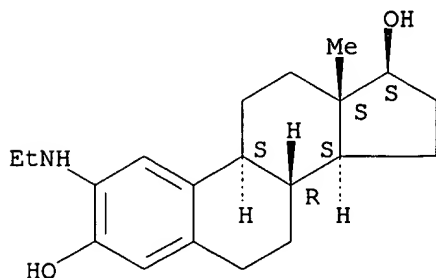
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(synthesis, antitubulin and antimitotic activity, and cytotoxicity of analogs of methoxyestradiol)

RN 165619-23-8 HCAPLUS

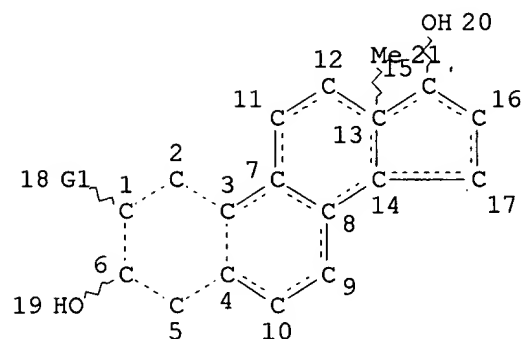
CN Estra-1,3,5(10)-triene-3,17-diol, 2-(ethylamino)-, (17 β .)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d que
L1

STR



N~N~N
@22 23 24

C≡C~G2
@25 26 27

Ak @

CH≡CH~G2
@28 29 30

Ak~CH≡CH2
@31 32 33

Ak~Cb~CH≡CH2
@34 35 36 37

C≡CH
@38 39

O~G2
@40 41

Ak~G3
@42 43

Ak~Cb~G3
@44 45 46

O~Ak~G3
@47 48 49

O~Ak~Cb~G3
@50 51 52 53

N~Et
@54 55

Ak~Cb
@61 62
O
||

Page 1-A
60

Page 1-B

N~C~Me
@56 57 58

Page 2-A
VAR G1=22/CN/25/28/31/34/38/40/42/44/47/50/54/56
VAR G2=60/61
VAR G3=OH/NH2/X/CF3
NODE ATTRIBUTES:

CONNECT IS E2 RC AT 2
CONNECT IS E2 RC AT 5
CONNECT IS E2 RC AT 10
CONNECT IS E2 RC AT 31
CONNECT IS E2 RC AT 34
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CONNECT IS E2 RC AT 42
CONNECT IS E2 RC AT 44
CONNECT IS E2 RC AT 45
CONNECT IS E2 RC AT 48

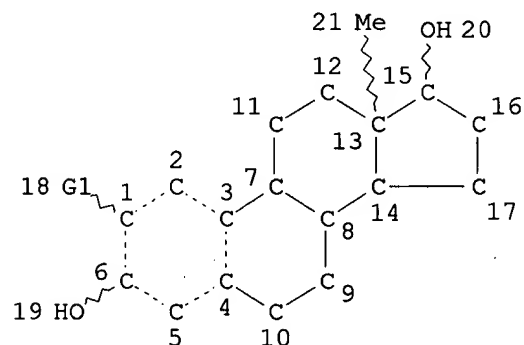
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 CONNECT IS E2 RC AT 54
 CONNECT IS E2 RC AT 56
 CONNECT IS E1 RC AT 60
 CONNECT IS E2 RC AT 61
 CONNECT IS E1 RC AT 62
 DEFAULT MLEVEL IS ATOM
 GGCAT IS UNS AT 35
 GGCAT IS UNS AT 45
 GGCAT IS UNS AT 52
 GGCAT IS UNS AT 62
 DEFAULT ECLEVEL IS LIMITED
 ECOUNT IS M6 C AT 35
 ECOUNT IS M6 C AT 45
 ECOUNT IS M6 C AT 52
 ECOUNT IS M6 C AT 62

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

L3 99 SEA FILE=REGISTRY SSS FUL L1
 L9 STR



N~N~N
 @22 23 24

C≡C~G2
 @25 26 27

Ak @

CH≡CH~G2
 @28 29 30

Ak~CH≡CH2
 @31 32 33

Ak~Cb~CH≡CH2
 @34 35 36 37

C≡CH
 @38 39

O~G2
 @40 41

Ak~G3
 @42 43

Ak~Cb~G3
 @44 45 46

O~Ak~G3
 @47 48 49

O~Ak~Cb~G3
 @50 51 52 53

N~Et
 @54 55

Ak~Cb
 @61 62
 O
 ||

Page 1-B

N~C~Me
@56 57 58

Page 2-A

VAR G1=22/CN/25/28/31/34/38/40/42/44/47/50/54/56

VAR G2=60/61

VAR G3=OH/NH2/X/CF3

NODE ATTRIBUTES:

CONNECT IS E2 RC AT 2

CONNECT IS E2 RC AT 5

CONNECT IS E2 RC AT 9

CONNECT IS E2 RC AT 10

CONNECT IS E2 RC AT 11

CONNECT IS E2 RC AT 12

CONNECT IS E3 RC AT 15

CONNECT IS E2 RC AT 16

CONNECT IS E2 RC AT 17

CONNECT IS E2 RC AT 31

CONNECT IS E2 RC AT 34

CONNECT IS E2 RC AT 35

CONNECT IS E2 RC AT 42

CONNECT IS E2 RC AT 44

CONNECT IS E2 RC AT 45

CONNECT IS E2 RC AT 48

CONNECT IS E2 RC AT 51

CONNECT IS E2 RC AT 52

CONNECT IS E2 RC AT 54

CONNECT IS E2 RC AT 56

CONNECT IS E1 RC AT 60

CONNECT IS E2 RC AT 61

CONNECT IS E1 RC AT 62

DEFAULT MLEVEL IS ATOM

GGCAT IS UNS AT 35

GGCAT IS UNS AT 45

GGCAT IS UNS AT 52

GGCAT IS UNS AT 62

DEFAULT ECLEVEL IS LIMITED

ECOUNT IS M6 C AT 35

ECOUNT IS M6 C AT 45

ECOUNT IS M6 C AT 52

ECOUNT IS M6 C AT 62

GRAPH ATTRIBUTES:

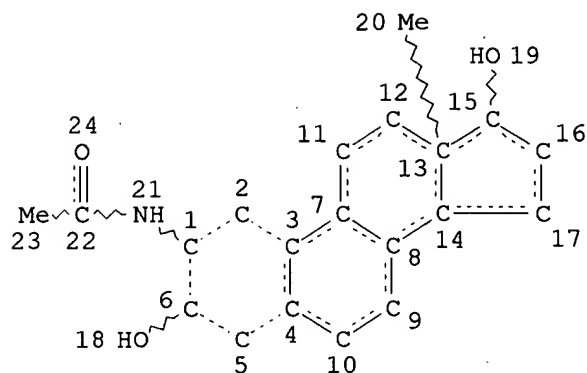
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 62

STEREO ATTRIBUTES: NONE

L10 40 SEA FILE=REGISTRY SUB=L3 SSS FUL L9

L26 STR



NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE

L27 1 SEA FILE=REGISTRY SUB=L10 SSS FUL L26

L28 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L27

=> d'ibib abs hitstr 1-2

L28 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:11127 HCAPLUS

DOCUMENT NUMBER: 136:64669

TITLE: Estrogenic compounds as antiangiogenic agents

INVENTOR(S): D'Amato, Robert J.; Varma, Ravi K.; Haugwitz, Rudiger G.; Cushman, Mark

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont. of U.S. Ser. No. 154,322, abandoned.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002002294	A1	20020103	US 2001-899702	20010705
PRIORITY APPLN. INFO.:			US 1997-59916P	P 19970924
			US 1998-154322	B1 19980916
OTHER SOURCE(S):		MARPAT 136:64669		
GI				

SOURCE: West Lafayette, IN, 47907, USA
 Journal of Medicinal Chemistry (1995), 38(12), 2041-9
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB In order to define the structural parameters assocd. with the antitubulin activity and cytotoxicity of 2-methoxyestradiol, a mammalian metabolite of estradiol, an array of analogs was synthesized and evaluated. The potencies of the new congeners as inhibitors of tubulin polymn. and colchicine binding were detd. using tubulin purified from bovine brain, and the cytotoxicities of the new compds. were studied in a variety of cancer cell cultures. Maximum antitubulin activity was obsd. in estradiols having unbranched chain substituents at the 2-position with three non-hydrogen atoms. 2-Ethoxyestradiol and 2-((E)-1-propenyl)estradiol were substantially more potent than 2-methoxyestradiol itself. The tubulin polymn. inhibitors in this series displayed significantly higher cytotoxicities in the MDA-MB-435 breast cancer cell line than in the other cell lines studied. The potencies of the analogs as cytotoxic and antimitotic agents in cancer cell cultures correlated with their potencies as inhibitors of tubulin polymn., supporting the hypothesis that inhibition of tubulin polymn. is the mechanism of the cytotoxic action of 2-methoxyestradiol and its congeners. Several of the more potent analogs were tested in an estrogen receptor binding assay, and their affinities relative to estradiol were found to be very low.

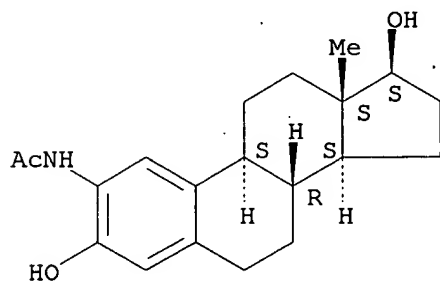
IT **165619-22-7P**

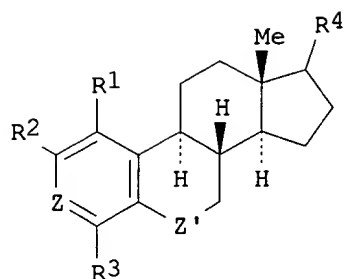
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
 (synthesis, antitubulin and antimitotic activity, and cytotoxicity of analogs of methoxyestradiol)

RN 165619-22-7 HCAPLUS

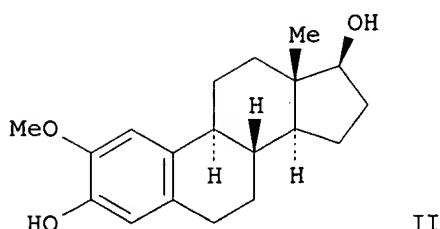
CN Acetamide, N-[(17.beta.)-3,17-dihydroxyestra-1,3,5(10)-trien-2-yl]- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry.





I



II

AB 2-Methoxyestradiol derivs., such as I [R1, R3 = H, Cl, Br, I, F, CN, alkyl, OH, CH2OH, NH2, alkylamino; R2 = N3, CN, C.tplbond.CR, C=CHR, RCH=CH2, C.tplbond.CH, OR, R-R1, OR-R1 (R = alkyl, R1 = OH, NH2, Cl, Br, I, F, CF3); Z = CH, COH, CR2-OH (R2 = alkyl, aralkyl); Z' = CH2, CO, CH(OH); C=NOH, C=NOR5, CHC.tplbond.N, CHNR5R5 (R5 = H, alkyl, aralkyl)], were used for treating mammalian disease characterized by undesirable angiogenesis. Thus, 2-methoxyestradiol (II) showed inhibition of tubulin polymn. (IC50 = 3.6.+-.0.4 .mu.M), inhibition of colchicine binding to tubulin (1.9.+-.0.2 .mu.M) and antitumor activity against breast, CNS, melanoma, ovarian tumor cell assay in vitro.

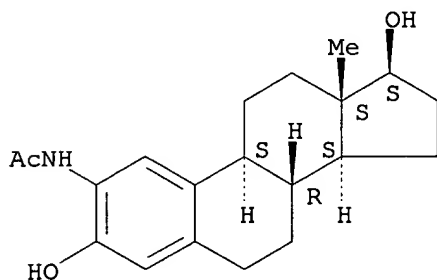
IT 165619-22-7, NSC 673651

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (estrogenic compds. as antiangiogenic agents)

RN 165619-22-7 HCAPLUS

CN Acetamide, N-[(17.beta.)-3,17-dihydroxyestra-1,3,5(10)-trien-2-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L28 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1995:592276 HCAPLUS

DOCUMENT NUMBER: 123:112496

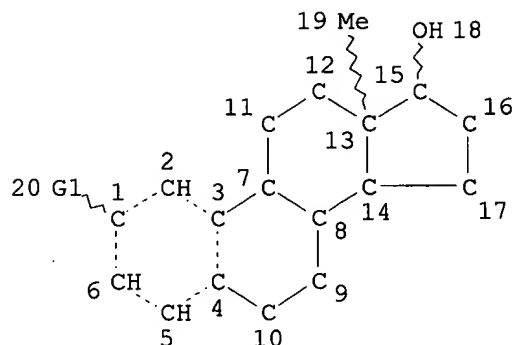
TITLE: Synthesis, Antitubulin and Antimitotic Activity, and Cytotoxicity of Analogs of 2-Methoxyestradiol, an Endogenous Mammalian Metabolite of Estradiol That Inhibits Tubulin Polymerization by Binding to the Colchicine Binding Site

AUTHOR(S): Cushman, Mark; He, Hu-Ming; Katzenellenbogen, John A.; Lin, Chii M.; Hamel, Ernest

CORPORATE SOURCE: Department of Medicinal Chemistry, Purdue University,

=> d que
L29

STR



O~Ak~G2
@21 22 23

O~Ak~Cb~G2
@24 25 26 27

VAR G1=21/24

VAR G2=OH/NH2/X/CF3

NODE ATTRIBUTES:

CONNECT IS E2 RC AT 22

CONNECT IS E2 RC AT 25

CONNECT IS E2 RC AT 26

DEFAULT MLEVEL IS ATOM

GGCAT IS UNS AT 26

DEFAULT ECLEVEL IS LIMITED

ECOUNT IS X10 C AT 22

ECOUNT IS X10 C AT 25

ECOUNT IS M6 C AT 26

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE

L31 0 SEA FILE=REGISTRY SSS FUL L29



STIC SEARCH RESULTS FEEDBACK FORM

Biotech-Chem Library

Questions about the scope or the results of the search? Contact *the searcher or contact:*

Mary Hale, Information Branch Supervisor
308-4258, CM1-1E01

Voluntary Results Feedback Form

➤ I am an examiner in Workgroup: Example: 1610

➤ Relevant prior art **found**, search results used as follows:

- ☐ 102 rejection
- ☐ 103 rejection
- ☐ Cited as being of interest.
- ☐ Helped examiner better understand the invention.
- ☐ Helped examiner better understand the state of the art in their technology.

Types of relevant prior art found:

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature
(journal articles, conference proceedings, new product announcements etc.)

➤ Relevant prior art **not found**:

- ☐ Results verified the lack of relevant prior art (helped determine patentability).
- ☐ Results were not useful in determining patentability or understanding the invention.

Comments:

Drop off or send completed forms to STIC/Biotech-Chem Library CM1 - Circ. Desk

